PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 213/75, A61K 31/44, C07C 235/56 — A1

(11) International Publication Number: WO 95/04046

(43) International Publication Date: 9 February 1995 (09.02.95)

(21) International Application Number: PCT/GB94/01631

(22) International Filing Date: 28 July 1994 (28.07.94)

(30) Priority Data:
9315595.0 28 July 1993 (28.07.93) GB

(71) Applicant *(for all designated States except US)*: RHONE-POULENC RORER LIMITED [GB/GB]; PRP House, St. Leonards Road, Eastbourne, East Sussex BN21 3YG (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MORLEY, Andrew, David [GB/GB]; Rhone-Poulenc Rorer Ltd., Dagenham, Essex RM10 7XS (GB). PALFREYMAN, Malcolm, Norman [GB/GB]; Rhone-Poulenc Rorer Ltd., Dagenham, Essex RM10 7XS (GB). RATCLIFFE, Andrew, James [GB/GB]; Rhone-Poulenc Rorer Ltd., Dagenham, Essex RM10 7XS (GB). SHARP, Brian, William [GB/GB]; Rhone-Poulenc Rorer Ltd., Dagenham, Essex RM10 7XS (GB).

(74) Agents: COLLIER, Jeremy, Austin, Grey et al.; J.A. Kemp & Co., 14 South Square, Gray's Inn, London WC1R 5LX (GB).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: COMPOUNDS AS PDE IV AND TNF INHIBITORS

(57) Abstract

This invention is directed to an [(ether or thioether)heteroaryl or aryl] compound or an N-oxide thereof or a pharmaceutically acceptable salt thereof, which is useful for inhibiting the production or physiological effects of TNF in the treatment of a patient suffering from a disease state associated with a physiologically detrimental excess of tumor necrosis factor (TNF). Compounds within the scope of the present invention also inhibit cyclic AMP phosphodiesterase, and are useful in treating a disease state associated with pathological conditions that are modulated by inhibiting cyclic AMP phosphodiesterase, such disease states including inflammatory and autoimmune diseases, in particular type IV cyclic AMP phosphodiesterase. The present invention is therefore directed to their pharmacological use for inhibiting TNF and/or cyclic AMP phosphodiesterase, pharmacological compositions comprising the compounds and methods for their preparation.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgystan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

COMPOUNDS AS PDE IV AND TNF INHIBITORS

Field of the Invention

This invention is directed to [(ether or thioether)heteroaryl or aryl] compounds, their preparation; pharmaceutical compositions containing these compounds, and their pharmaceutical use in the treatment of disease states associated with proteins that mediate cellular activity.

Disease states associated with abnormally high physiological levels of cytokines such as TNF are treatable according to the invention. TNF is an important pro-inflammatory cytokine which causes hemorrhagic necrosis of tumors and possesses other important biological activities. TNF is released by activated macrophages, activated T-lymphocytes, natural killer cells, mast cells and basophils, fibroblasts, endothelial cells and brain astrocytes among other cells.

The principal in vivo actions of TNF can be broadly classified as inflammatory and catabolic. It has been implicated as a mediator of endotoxic shock, inflammation of joints and of the airways, immune deficiency states, allograft rejection, and in the cachexia associated with malignant disease and some parasitic infections. In view of the association of high serum levels of TNF with poor prognosis in sepsis, graft versus host disease and acute respiratory distress syndrome, and its role in many other immunological processes, this factor is regarded as an important mediator of general inflammation.

TNF primes or activates neutrophils, eosinophils, fibroblasts and endothelial cells to release tissue damaging mediators. TNF also activates monocytes, macrophages and T-lymphocytes to cause the production of

colony stimulating factors and other pro-inflammatory cytokines such IL_1, IL_6, IL_8 and GM-CSF, which in some case mediate the end effects of TNF. The ability of TNF to activate T-lymphocytes, monocytes, macrophages and related cells has been implicated in the progression of Human Immunodeficiency Virus (HIV) infection. In order for these cells to become infected with HIV and for HIV replication to take place the cells must be maintained in an activated state. Cytokines such as TNF have been shown to activate HIV replication in monocytes and macrophages. Features of endotoxic shock such as fever, metabolic acidosis, hypotension and intravascular coagulation are thought to be mediated through the actions of TNF on the hypothalamus and in reducing the anti-coagulant activity of vascular endothelial cells. The cachexia associated with certain disease states is mediated through indirect effects on protein catabolism. TNF also promotes bone resorption and acute phase protein synthesis.

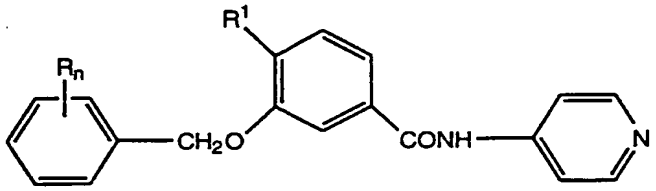
The discussion herein related to disease states associated with TNF include those disease states related to the production of TNF itself, and disease states associated with other cytokines, such as but not limited to IL-1, or IL-6, that are modulated by association with TNF. For example, an IL-1 associated disease state, where IL-1 production or action is exacerbated or secreted in response to TNF, would therefore be considered a disease state associated with TNF. TNF-alpha and TNF-beta are also herein referred to collectively as "TNF" unless specifically delineated otherwise, since there is a close structural homology between TNF-alpha (cachectin) and TNF-beta (lymphotoxin) and each of them has a capacity to induce similar biologic responses and bind to the same cellular receptor.

Disease states associated with pathological conditions that are modulated by inhibiting enzymes, which are associated with secondary cellular messengers, such as cyclic AMP phosphodiesterase, are also treatable according to the invention Cyclic AMP phosphodiesterase is an important enzyme which regulates cyclic AMP levels and in turn thereby regulates other important biological reactions. The ability to regulate cyclic AMP phosphodiesterase, including type IV cyclic AMP phosphodiesterase, therefore, has been implicated as being capable of treating assorted biological conditions.

In particular, inhibitors of type IV cyclic AMP phosphodiesterase have been implicated as being bronchodilators and asthma-prophylactic agents and as agents for inhibiting eosinophil accumulation and of the function of eosinophils, and for treating other diseases and conditions characterized by, or having an etiology involving, morbid eosinophil accumulation. Inhibitors of cyclic AMP phosphodiesterase are also implicated in treating inflammatory diseases, proliferative skin diseases and conditions associated with cerebral metabolic inhibition.

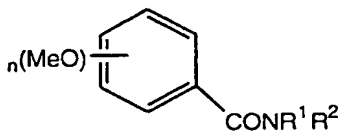
Reported Developments

Chemical Abstracts, 108(15), April 11, 1988, abstract no. 131583p pertains to an abstract of Japanese Patent Application Publication No. JP-A-62 158,253 which discloses that a substituted phenyl compound of formula



is a cardiotonic, but does not disclose or suggest that the compound inhibits cyclic AMP phosphodiesterase or TNF. JP-A-62 158,253 also does not disclose or suggest that the moiety that is ortho to R^1 may be anything other than benzyloxy.

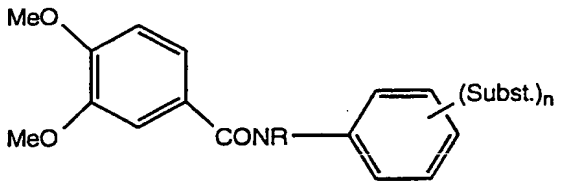
Chemical Abstracts, 99(6), August 8, 1983, abstract no. 43556z pertains to an abstract of Japanese Patent Application Publication No. JP-A-5 869,812 which discloses that a phenyl compound of formula



is a hypoglycemic agent, but does not disclose or suggest that the compound inhibits cyclic AMP phosphodiesterase or TNF. JP-A-5 869,812 also does not

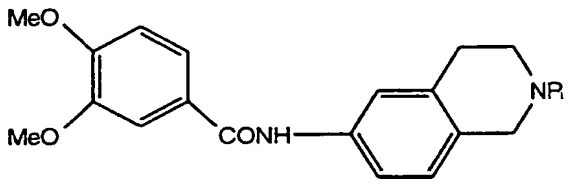
disclose or suggest that the benzamido moiety may be substituted by anything other than methoxy.

Panos Grammaticakis, Bull. Soc. Chim. Fr., 848-857 (1965) discloses a phenyl compound of the formula



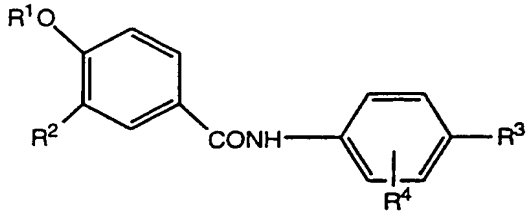
Grammaticakis examines the ultraviolet and visible absorbances of compounds bearing different substituents. Grammaticakis does not disclose or suggest that the compound exhibits any pharmacological activity. JP-A-5 869,812 also does not disclose or suggest that the benzamido moiety may be substituted by anything other than methoxy.

Ian W. Mathison, et al., J. Med. Chem., 16(4), 332-336 (1973), discloses that a phenyl compound of formula



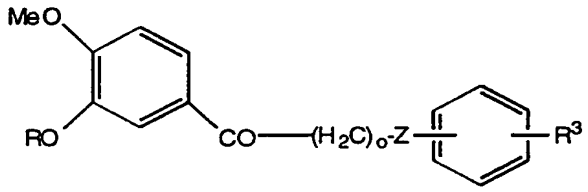
is a hypotensive agent, but do not disclose or suggest that the compound inhibits cyclic AMP phosphodiesterase or TNF. Mathison, et al., also do not disclose or suggest that the benzamido moiety may be substituted by anything other than methoxy.

European Patent Application Publication No. EP 232199 B1 discloses that phenyl compounds of formula

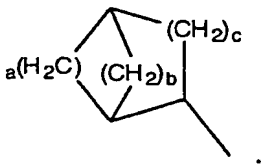


wherein R^2 is alpha,alpha'-disubstituted alkyl or mono- or polycyclic cycloalkyl bonded to the phenyl moiety via a quaternary carbon, exhibit anti-inflammatory and/or anti-allergic activity. EP 232199 B1 does not disclose or suggest compounds wherein R^2 is alkyl bonded to the phenyl moiety via a nonquaternary carbon, alkenyl, alkynyl, cyclothioalkyl or cyclothioalkenyl, or R^3 is azaheteroaryl having a nitrogen atom thereof oxidised to the corresponding N-oxide moiety.

European Patent Application Publication No. EP 470,805 A1 discloses phenyl compounds of the formula



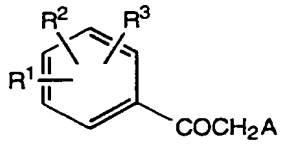
wherein R may be C_{3-7} alkyl, C_{3-7} cycloalkyl or



;

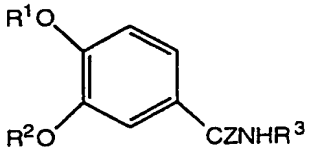
Z may be a bond; o is 1-4; a and b are independently 1-3; and c is 0-2. EP 470,805 A1 discloses that these compounds are useful intermediates for preparing PDE IV inhibitors, but does not disclose or suggest that the compounds have any pharmacological activity. EP 470,805 A1 furthermore does not disclose or suggest compounds wherein R or the methyl moiety is directly bonded to the phenyl moiety.

Japanese Patent Application Publication No. JP-A-0 4360847 discloses compounds of the formula



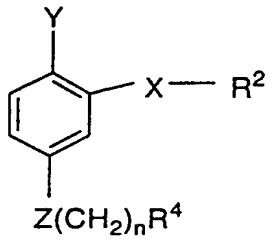
wherein R^1, R^2 and R^3 may be the same or different and may be halo or lower alkoxy or lower alkyl both optionally substituted by halo; and A may be optionally substituted aryl or 5-6 membered heterocyclyl group. JP-A-0 4360847 discloses that the compounds are useful intermediates for preparing antimicrobial agents, but does not disclose or suggest that the compounds have any pharmacological activity. JP-A-0 4360847 also does not disclose or suggest that the compounds wherein the phenylacyl moiety is substituted in the 3,4-positions relative to the acyl moiety by lower alkoxy groups. Furthermore, JP-A-0 4360847 does not disclose or suggest compounds wherein R^2 is alkenyl, alkynyl, cyclothioalkyl or cyclothioalkenyl or R^3 is azaheteroaryl having a nitrogen atom thereof oxidised to the corresponding N-oxide moiety.

WO Patent Application No. 92/12961 discloses that compounds of the formula



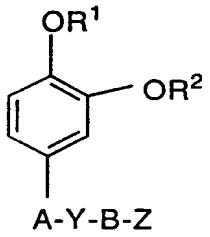
inhibit cyclic AMP phosphodiesterase. WO Patent Application No. 92/12961 does not disclose or suggest that these compound inhibit TNF. WO Patent Application No. 92/12961 does not disclose or suggest compounds wherein R^1 or R^2 is directly bonded to the phenyl moiety.

WO Patent Application No. 93/25517 discloses that compounds of the following formula inhibit PDE IV. WO Patent Application No. 93/25517 does



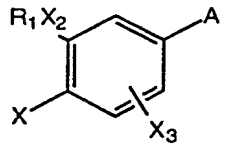
not disclose or suggest that these compound inhibit TNF. WO Patent Application No. 93/25517 does not disclose or suggest compounds wherein X is a direct bond and R^2 is alkyl, alkenyl, alkynyl, cyclothioalkyl or cyclothioalkenyl, or R^3 is azaheteroaryl having a nitrogen atom thereof oxidised to the corresponding N-oxide moiety.

WO Patent Application No. 93/10228 discloses that compounds of the following formula

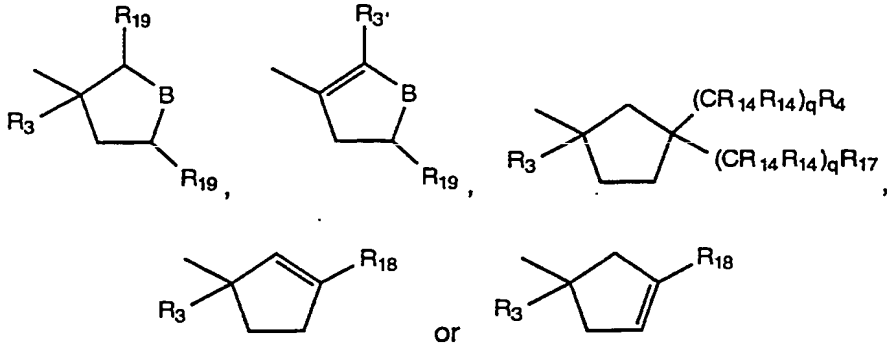


inhibit PDE IV and as such are useful in treatment of inflammatory diseases. WO Patent Application No. 93/10228 does not disclose or suggest that these compounds inhibit TNF. WO Patent Application No. 93/10228 does not disclose or suggest compounds wherein R^1 or R^2 is directly bonded to the phenyl moiety.

WO Patent Application No. 93/07111 discloses that compounds of the following formula wherein X may be YR_2; Y is O or $S(O)_m$; X_3 is halogen or

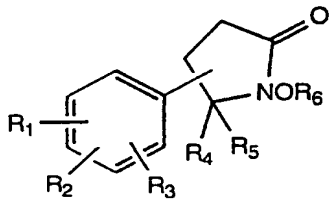


hydrogen; and A is a group of formula



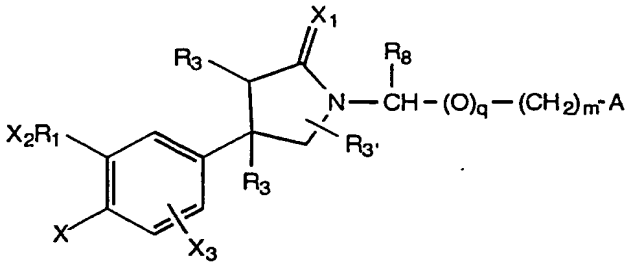
inhibit PDE IV. WO Patent Application No. 93/07111 does not disclose or suggest compounds wherein the A substituent is a [(-CXNH- or -$CXCH_2$-)aryl or heteroaryl] moiety wherein X is O or S.

WO Patent Application No. 91/16303 discloses that compounds of the following formula wherein R_1, R_2 and R_3 may be hydrogen, halogen, lower alkyl,



lower alkoxy or cycloalkoxy inhibit PDE IV. WO Patent Application No. 91/16303 does not disclose or suggest compounds wherein the lactam moiety is substituted by a [(-CXNH- or -$CXCH_2$-)aryl or heteroaryl] moiety wherein X is O or S.

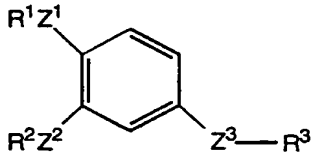
WO Patent Application No. 92/19594 discloses that compounds of the following formula wherein X may be YR_2; Y is O or $S(O)_m$; and X_3 may be



hydrogen or halogen inhibit PDE IV. WO Patent Application No. 92/19594 does not disclose or suggest compounds wherein the lactam moiety is substituted by a [(-CXNH- or -$CXCH_2$-)aryl or heteroaryl] moiety wherein X is O or S.

SUMMARY OF THE INVENTION

This invention is directed to a compound of formula I, which is useful for inhibiting the production or physiological effects of TNF in the treatment of a patient suffering from a disease state associated with a physiologically detrimental excess of tumor necrosis factor (TNF), where formula I is as follows:



I

wherein

R^1 is lower alkyl;

R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cyclothioalkyl or cyclothioalkenyl;

R^3 is aryl or heteroaryl;

Z^1 and Z^2 are independently oxygen, sulfur or direct bond, and only one of Z^1 and Z^2 is a direct bond;

Z^3 is -CZCH$_2$- or -CZNH-; and

Z is oxygen or sulfur,

or N-oxide thereof or a pharmaceutically acceptable salt thereof,

provided that

when Z^2 is a direct bond, R^2 is alkyl bonded to the phenyl moiety via a nonquaternary carbon, alkenyl, alkynyl, cyclothioalkyl or cyclothioalkenyl, or R^3 is azaheteroaryl having a nitrogen atom thereof oxidised to the corresponding N-oxide moiety.

Compounds within the scope of the present invention also inhibit cyclic AMP phosphodiesterase, and are useful in treating a disease state associated with pathological conditions that are modulated by inhibiting cyclic AMP phosphodiesterase, such disease states including inflammatory and autoimmune diseases, in particular type IV cyclic AMP phosphodiesterase. The present invention is therefore directed to their pharmacological use, pharmacological compositions comprising the compounds and methods for their preparation.

DETAILED DESCRIPTION OF THE INVENTION

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

Definitions

"Patient" includes both human and other mammals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched having about 1 to about 15 carbon atoms in the chain. Preferred alkyl groups have 1 to about 12 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are

attached to a linear alkyl chain. "Lower alkyl" means about 1 to about 4 carbon atoms in the chain which may be straight or branched. The alkyl group is optionally substituted by one or more of halo, cycloalkyl, cycloalkenyl or cycloalkylidene groups. Exemplary alkyl groups include methyl, fluoromethyl, difluoromethyl, trifluoromethyl, cyclopropylmethyl, cyclopentylmethyl, cyclopentylfluoromethyl, cyclopentylidenemethyl, ethyl, fluoroethyl,*n*-propyl, *i*-propyl, *n*-butyl, *t*-butyl, *n*-pentyl, 3-pentyl, heptyl, octyl, nonyl, decyl and dodecyl; preferred are methyl, ethyl, difluoromethyl, fluoroethyl, cyclopentylmethyl and cyclopentylfluoromethyl.

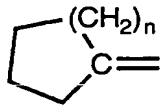
"Alkenyl" means an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. The alkenyl group is optionally substituted by one or more halo, cycloalkyl or cycloalkenyl. Exemplary alkenyl groups include ethenyl, propenyl, *n*-butenyl, *i*-butenyl, 3-methylpropenyl, *n*-pentenyl, heptenyl, octenyl and decenyl.

"Alkynyl" means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched having about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 4 carbon atoms in the chain which may be straight or branched. The alkynyl group is optionally substituted by one or more halo, cycloalkyl or cycloalkenyl. Exemplary alkynyl groups include ethynyl, propynyl, *n*-butynyl, 2-butynyl, 3-methylbutynyl, *n*-pentynyl, heptynyl, octynyl and decynyl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system of about 3 to about 10 carbon atoms. The cycloalkyl group is optionally substituted by one or more halo, methylidene ($H_2C=$) or alkyl. Exemplary

monocyclic cycloalkyl rings include cyclopentyl, fluorocyclopentyl, cyclohexyl and cycloheptyl; more preferred is cyclopentyl. Exemplary multicyclic cycloalkyl rings include 1-decalin, adamant-(1- or 2-)yl, trinorbornyl and tricyclo[2.2.1.$0^{2,6}$.]heptyl.

"Cycloalkylidene" means a non-aromatic monocyclic ring system of about 5 to about 7 carbon atoms of formula



wherein n is 1 to 3.

"Cycloalkenyl" means a non-aromatic monocyclic or multicyclic ring system containing a carbon-carbon double bond and having about 3 to about 10 carbon atoms. The cycloalkenyl group is optionally substituted by one or more halo, alkyl and methylidene (CH_2=). Preferred monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl; more preferred is cyclopentenyl. A preferred multicyclic cycloalkenyl ring is a norbornylenyl.

"Cyclothioalkyl" means a non-aromatic monocyclic or multicyclic ring system of about 3 to about 10 ring atoms wherein at least one of the ring atoms is sulfur and the other ring atoms are carbon. Preferred rings include about 5 to about 6 ring atoms. Also preferred are rings in which one or two of the ring atoms is/are sulfur. The cyclothioalkyl is optionally substituted by one or more halo. The thio moiety of the cyclothioalkyl ring may also be optionally oxidized to the corresponding S-oxide or S,S-dioxide. Preferred monocyclic cyclothioalkyl rings include tetrahydrothiophenyl and tetrahydrothiopyranyl; more preferred is tetrahydrothiophenyl.

"Cyclothioalkenyl" means a non-aromatic monocyclic or multicyclic ring system having about 3 to about 10 ring atoms wherein at least one of the ring atoms is sulfur and the other ring atoms are carbon and the ring system contains a carbon-carbon double bond. Preferred rings include about 5 to about 6 ring atoms. Also preferred are rings in which one or two of the ring atoms is/are sulfur. The cyclothioalkenyl is optionally substituted by one or

more halo. The thio moiety of the cyclothioalkenyl may also be optionally oxidized to the corresponding S-oxide or S,S-dioxide. Preferred monocyclic cyclothioalkyl rings include dihydrothiophenyl and dihydrothiopyranyl; more preferred is dihydrothiophenyl.

"Aromatic" means aryl or heteroaryl as defined below. Preferred aromatic groups include phenyl, halo substituted phenyl and azaheteroaryl.

"Aryl" means aromatic carbocyclic radical containing about 6 to about 10 carbon atoms. Exemplary aryl include phenyl or naphthyl, or phenyl or naphthyl substituted with one or more aryl group substituents which may be the same or different, where "aryl group substituent" includes hydrogen, alkyl, aryl, aralkyl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkyloxy, carboxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, acylamino, aroylamino, alkylsulfonyl, arylsulfonyl, alkylsulfinyl, arylsulfinyl, alkylthio, arylthio, aralkylthio, Y^1Y^2N-, Y^1Y^2NCO- or $Y^1Y^2NSO_2$-, where Y^1 and Y^2 are independently hydrogen, alkyl, aryl, and aralkyl. Preferred aryl group substituents include hydrogen, alkyl, hydroxy, acyl, aroyl, halo, nitro, cyano, alkoxycarbonyl, acylamino, alkylthio, Y^3Y^4N-, Y^3Y^4NCO- and $Y^3Y^4NSO_2$-, where Y^3 and Y^4 are independently hydrogen and alkyl.

"Heteroaryl" means about a 5- to about a 10- membered aromatic monocyclic or multicyclic hydrocarbon ring system in which one or more of the carbon atoms in the ring system is/are element(s) other than carbon, for example nitrogen, oxygen or sulfur. The heteroaryl may also be substituted by one or more aryl group substituents. "Azaheteroaryl" means a subclass of heteroaryl wherein one or more of the atoms in the ring system is/are replaced by nitrogen. Imine nitrogen (=N-) moieties of an azaheteroaryl group may also be in an oxidized state such as the corresponding N-oxide. Exemplary heteroaryl groups include pyrazinyl, furanyl, thienyl, pyridyl, pyrimidinyl, isoxazolyl, isothiazolyl, pyridazinyl, 1,2,4-triazinyl, quinolinyl, and isoquinolinyl. Preferred heteroaryl groups include pyrazinyl, thienyl, pyridyl, pyrimidinyl, isoxazolyl and isothiazolyl. Preferred azaheteroaryl groups include pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl or 1,2,4-triazinyl.

"Aralkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls contain a lower alkyl moiety. Exemplary aralkyl groups include benzyl, 2-phenethyl and naphthlenemethyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Exemplary hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-CO- or alkyl-CO- group in which the alkyl group is as previously described. Preferred acyls contain a lower alkyl. Exemplary acyl groups include formyl, acetyl, propanoyl, 2-methylpropanoyl, butanoyl and palmitoyl.

"Aroyl" means an aryl-CO- group in which the aryl group is as previously described. Exemplary groups include benzoyl and 1- and 2-naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Exemplary alkoxy groups include methoxy, ethoxy, *n*-propoxy, *i*-propoxy, *n*-butoxy and heptoxy.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Exemplary aryloxy groups include phenoxy and naphthoxy.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl groups is as previously described. Exemplary aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Exemplary alkylthio groups include methylthio, ethylthio, *i*-propylthio and heptylthio.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Exemplary arylthio groups include phenylthio and naphthylthio.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. An exemplary aralkylthio group is benzylthio.

"Y^3Y^4N-" means a substituted or unsubstituted amino group, wherein Y^3 and Y^4 are as previously described. Exemplary groups include amino (H_2N-), methylamino, ethylmethylamino, dimethylamino and diethylamino.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Exemplary alkoxycarbonyl groups include methoxy- and ethoxycarbonyl.

"Aryloxycarbonyl" means an aryl-O-CO- group. Exemplary aryloxycarbonyl groups include phenoxy- and naphthoxycarbonyl.

"Aralkyloxycarbonyl" means an aralkyl-O-CO- group. An exemplary aralkyloxycarbonyl group is benzyloxycarbonyl.

"Y^1Y^2NCO-" means a substituted or unsubstituted carbamoyl group, wherein Y^1 and Y^2 are as previously described. Exemplary groups are carbamoyl (H_2NCO-) and dimethylcarbamoyl (Me_2NCO-).

"$Y^1Y^2NSO_2$-" means a substituted or unsubstituted sulfamoyl group, wherein Y^1 and Y^2 are as previously described. Exemplary groups are sulfamoyl (H_2NSO_2-) and dimethylsulfamoyl (Me_2NSO_2-).

"Acylamino" is an acyl-NH- group wherein acyl is as defined herein.

"Aroylamino" is an aroyl-NH- group wherein aroyl is as defined herein.

"Alkylsulfonyl" means an alkyl-SO_2- group. Preferred groups are those in which the alkyl group is lower alkyl.

"Alkylsulfinyl" means an alkyl-SO- group. Preferred groups are those in which the alkyl group is lower alkyl.

"Arylsulfonyl" means an aryl-SO_2- group.

"Arylsulfinyl" means an aryl-SO- group.

"Halo" means fluoro, chloro, bromo, or iodo. Preferred are fluoro, chloro or bromo; more preferred are fluoro or chloro, and further preferred is fluoro.

"N-oxide" means a moiety of the following structure  .

Preferred Embodiments

A compound of formula I is preferred for use in treating a disease state associated with a physiologically detrimental excess of tumor necrosis factor. Disease states associated with pathological conditions that are modulated by inhibiting tumor necrosis factor are treatable with a compound of formula I.

A compound of formula I is also preferred for use in treating a disease state associated with a physiologically detrimental excess of cyclic AMP phosphodiesterase. Disease states associated with pathological conditions that are modulated by inhibiting cyclic AMP phosphodiesterase are treatable with a compound of formula I.

According to a compound aspect of the invention, preferred compounds are described formula I,

wherein

R^2 is alkyl, alkenyl or cycloalkyl;

R^3 is phenyl, substituted phenyl or azaheteroaryl;

Z^1 and Z^2 are independently oxygen or direct bond, and only one of Z^1 and Z^2 is a direct bond; and

Z^3 is $-COCH_2-$ or -CONH-.

According to a further compound aspect of the invention, preferred compounds are described formula I,

wherein

R^1 is methyl, ethyl, fluoroethyl or difluoromethyl;

R^2 is 2-methylpropenyl, cyclopentylfluoromethyl, cyclopentylmethyl, cyclopentyl or trinorbornyl; and

R^3 is azaheteroaryl.

According to a further aspect of the invention, preferred are N-oxide compounds of formula I, that is compounds of formula I wherein R^3 is azaheterocyclyl having an imine moiety thereof as an N-oxide. Also futher preferred are compounds of formula I wherein R^3 is 3,5-dihalo-1-oxido-4-pyridinium.

Compounds of the invention wherein R^1 is lower alkyl optionally substituted by one or more halo, preferably fluoro, are also preferred. Compounds of the invention wherein R^2 is substituted by one or more halo, preferably fluoro, are also preferred. It is further preferred that the halo substitution is on a position of R^1 or R^2 that is attached respectively to Z^1 and Z^2. Where R^2 is cyclothioalkyl or cyclothioalkenyl substituted by halo, it is also preferred that the halo substitution is on a position adjacent to the thio moiety of the cyclothioalkyl or cyclothioalkenyl.

Among the compounds of the invention wherein R^3 is substituted phenyl, the phenyl group is preferably substituted on the 2-position or on both the 2- and 6-positions; more preferably on both the 2- and 6-positions. It is also preferred that the phenyl substituent is halo; preferably chloro or fluoro.

Similarly, among compounds of the invention where R^3 is substituted heteroaryl, the heteroaryl group is preferably substituted on one or both, more preferably on both, of the positions adjacent to a position of R^3 that is attached to Z^3.

Special embodiments of the compounds of the invention include those of formula I wherein R^3 is azaheteroaryl substituted on one or both, more

preferably on both, of the positions adjacent to a position of R^3 that is attached to Z^3, or an N-oxide thereof. Further preferred are compounds wherein R^3 is a 3,5-dihalopyrid-4-yl moiety, preferably wherein halo is chloro or fluoro, or an N-oxide thereof.

Special embodiments of the compounds of the invention also include those of formula I wherein Z^3 is -CZNH-, more preferably wherein Z is oxygen.

Special embodiments of the compounds of the present invention include those wherein R^2 is 2-methylpropenyl, cyclopentylfluoromethyl, cyclopentylmethyl, cyclopentyl, cyclopentylidenemethyl, trinorbornyl, trinorbornenyl, tricyclo[2.2.1.$0^{2,6}$.]heptanyl or tetrahydrothiophenyl; more preferred 2-methylpropenyl, cyclopentylfluoromethyl, cyclopentylmethyl, cyclopentyl, cyclopentylidenemethyl and trinorbornyl.

Another special embodiment of the compounds of the invention include those of formula I wherein R^1 is lower alkyl optionally substituted by halo, preferably fluoro; and R^2 is 2-methylpropenyl, cyclopentylfluoromethyl, cyclopentylmethyl, cyclopentyl and trinorbornyl.

According to a further aspect of the invention, preferred compounds of formula I are described wherein Z^1 is oxygen and Z^2 is a direct bond; Z^1 is sulfur and Z^2 is a direct bond; and Z^1 is a direct bond and Z^2 is oxygen are preferred; and more preferred are Z^1 is oxygen and Z^2 is a direct bond.

Preferred compounds for use according to the invention are selected from the following:

(A) N-(3,5-dichloropyrid-4-yl)-3-cyclopentylmethyl-4-methoxybenzamide;

(B) N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-ethylbenzamide;

(C) N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-methylbenzamide;

(D) N-(3,5-dichloro-1-oxido-4-pyridinio) 3-cyclopentylmethyl-4-methoxybenzamide;

(E) N-(3,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentyloxy-4-ethylbenzamide;

(F) N-(3,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentyloxy-4-methylbenzamide;

(G) N-(,5-dichloro-1-oxido-4-pyridinio)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-ethylbenzamide;

(H) N-(,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentylidenemethyl-4-methoxybenzamide;

(I) N-(,5-dichloro-1-oxido-4-pyridinio)-3-(2-methylpropenyl)-4-methoxybenzamide;

(J) N-(,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentylidenemethyl-4-difluoromethoxybenzamide;

(K) N-(,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentylfluoromethyl-4-methoxybenzamide;

(L) N-(,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentyloxy-4-(1-fluoroethyl)benzamide;

(M) N-(3,5-dichloropyrid-4-yl)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-ethylbenzamide;

(N) N-(3,5-dichloropyrid-4-yl)-3-cyclopentylidenemethyl-4-methoxybenzamide;

(O) N-(3,5-dichloropyrid-4-yl)-3-(2-methylpropenyl)-4-methoxybenzamide;

(P) N-(3,5-dichloropyrid-4-yl)-3-cyclopentylidenemethyl-4-difluoromethoxybenzamide;

(Q) N-(3,5-dichloropyrid-4-yl)-3-cyclopentylfluoromethyl-4-methoxybenzamide; and

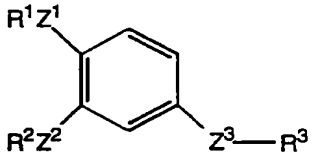
(R) N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-(1-fluoroethyl)benzamide.

Preferred compounds include A-R; more preferred are ?.

The letters A-R are allocated to compounds for easy reference in this specification.

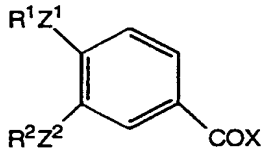
Compounds of formula I may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature.

Thus, compounds of formula I wherein R^1, R^2, R^3, Z^1 and



I

Z^2 are as hereinbefore defined, Z^3 represents a -CZNH- linkage, and Z is oxygen, may be prepared by the reaction of compounds of formula II



II

wherein R^1, R^2, Z^1 and Z^2 are as hereinbefore defined, and X represents halo, such as bromo or, preferably, chloro, with a compound of the formula III

$$R^3NH_2 \qquad \text{III}$$

wherein R^3 is as hereinbefore defined, preferably in the presence of a base such as an alkali metal hydride, such as sodium hydride, or an amine, preferably a tertiary amine, such as triethylamine or pyridine, optionally in an inert solvent, for example dichloromethane, dimethylformamide, or an ether,

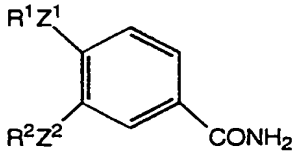
such as diethyl ether or tetrahydrofuran, preferably at a temperature from about 0°C to the reflux temperature or at the melting point of the reaction mixture.

Alternatively, compounds of formula I wherein R^1, R^2, R^3, Z^1 and Z^2 are as hereinbefore defined, Z^3 represents a -CZNH- linkage, and Z represents oxygen, may be prepared by the reaction of compounds of formula II as hereinbefore described, with a compound of the formula IV wherein R^3 is as

$$R^4CONHR^3 \qquad IV$$

hereinbefore defined, and R^4 represents an alkyl or cycloalkyl group containing up to 5 carbon atoms, preferably a methyl group, preferably in the presence of a base, for example an alkali metal hydride, such as sodium hydride, or an amine, preferably a tertiary amine, such as triethylamine, in an inert solvent, for example toluene, dimethylformamide, or an ether, such as tetrahydrofuran or diethyl ether, at a temperature from about 0°C to reflux, then a second base, for example an amine, such as piperidine.

Alternatively, compounds of formula I, wherein R^1, R^2, R^3, Z^1 and Z^2 are as hereinbefore defined, Z is oxygen, and Z^3 represents a -CZNH- linkage, may be prepared by the reaction of compounds of formula V wherein R^1, R^2,



V

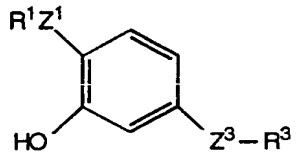
Z^1 and Z^2 are as hereinbefore defined, with compounds of formula VI wherein

$$R^3X \qquad VI$$

R^3 and X are as hereinbefore defined, preferably X is chloro, and preferably the preparation takes place in the presence of a base, for example an alkali metal hydride, such as sodium hydride, an alkali metal alkoxide, such as potassium t-butoxide, an alkali metal hydroxide, such as sodium hydroxide or carbonate, or an amine, preferably a tertiary amine, such as triethylamine or pyridine, optionally in an inert solvent, for example dichloromethane,

dimethylformamide, or an ether, such as diethyl ether or tetrahydrofuran, preferably at a temperature from about 0°C to reflux.

Alternatively, compounds of formula I, wherein R^1, R^2 and R^3 are as hereinbefore defined, Z^1 is a direct bond, Z^3 represents a -CZNH- linkage, and Z and Z^2 are oxygen, may be prepared by the reaction of compounds of formula VII wherein R^1, R^3, Z and Z^1 are as hereinbefore defined and Z^3



VII

represents a -CZNH- linkage, and Z is oxygen, with compounds of the formula VIII wherein R^2 is as hereinbefore defined, preferably, X is as hereinbefore

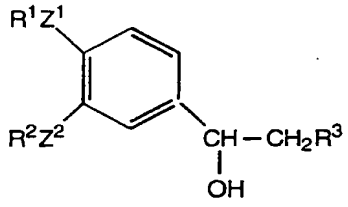
$$R^2X \qquad VIII$$

defined or *p*-toluenesulfonate, preferably X is bromo, and preferably the preparation takes place in the presence of a base, for example an alkali metal hydride, such as sodium hydride, an alkali metal hydroxide or carbonate, such as sodium hydroxide or carbonate, or an amine, preferably a tertiary amine, such as. triethylamine or pyridine, optionally in an inert solvent, for example dichloromethane, dimethylformamide, or an ether, such as diethyl ether or tetrahydrofuran, preferably at a temperature from about 0°C to reflux, or by the reaction of the compound of formula VII above with compounds of the formula IX, wherein R^2 is as hereinabove defined in the presence of, for example,

$$R^2OH \qquad IX$$

diisopropylazodicarboxylate and triphenylphosphine.

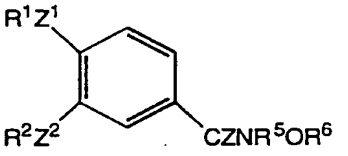
Alternatively, compounds of formula I, wherein R^1, R^2, R^3, Z^1 and Z^2 are as hereinbefore defined, Z^3 represents a -$CZCH_2$- linkage, and Z represents oxygen, are prepared from compounds of formula X wherein R^1, R^2, R^3, Z^1



X

and Z^2 are as hereinbefore defined, by oxidation by the application or adaptation of known methods. The oxidation is carried out, for example, by reaction with oxalyl chloride and dimethyl sulfoxide, in the presence of a base, preferably a tertiary amine, preferably triethylamine, in an inert solvent such as dichloromethane, at temperatures from about -60°C to about room temperature, preferably at a reduced temperature, or by adaptation of known methods for the preparation of ketone from a secondary alcohol, for example the application of pyridinium dichromate. Alternatively, the oxidation is carried out by reaction with chromium trioxide in the presence of 3,5-dimethylpyrazole.

According to a further feature of the present invention, compounds of formula I, wherein R^1, R^2, R^3, Z, Z^1 and Z^2 are as hereinbefore defined, Z^3 represents a -$CZCH_2$- linkage, and preferably those wherein Z represents oxygen, are prepared from compounds of formula XI wherein R^1, R^2, Z,



XI

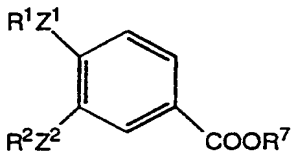
Z^1 and Z^2, are as hereinbefore defined and R^5 and R^6 represent lower alkyl, such as methyl, groups, by coupling with compounds of the formula XII wherein

$$R^3CH_3 \qquad \text{XII}$$

R^3 is as hereinbefore defined, in the presence of a strong base such as lithium diisopropylamide (usually prepared in situ from *n*-butyl lithium and diisopropylamine), preferably at a low temperature.

Alternatively, compounds of formula I, wherein R^1, R^2, R^3, Z^1 and Z^2 are as hereinbefore defined, Z^3 represents a -$CZCH_2$- linkage, and Z

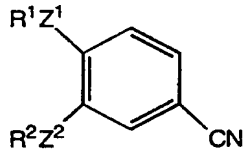
represents oxygen, are prepared from compounds of formula XIII wherein R^1, R^2, Z^1 and



XIII

Z^2 are as hereinbefore defined, and R^7 is alkyl, cycloalkyl or aralkyl containing up to 8 carbon atoms, by coupling with compounds of the formula XII above, wherein R^3 is as hereinbefore defined, in the presence of a strong base, such as an alkali metal amide or alkyl, for example *n*-butyl lithium or lithium diisopropylamide (usually prepared in situ from butyl lithium and diisopropylamine), in an inert solvent, for example cyclohexane or an ether, such as tetrahydrofuran or diethyl ether, at a temperature from about -78°C to about room temperature.

According to a feature of the present invention, compounds of formula I, wherein R^1, R^2, R^3, Z^1 and Z^2 are as hereinbefore defined, Z^3 represents a $-CZCH_2-$ linkage, and Z represents oxygen, are prepared by the reaction of compounds of formula XIV, wherein R^1, R^2, Z^1 and Z^2 are as hereinbefore



XIV

defined, are as hereinbefore defined, with compounds of the formula XV

$$R^3CH_2MgX \qquad XV$$

wherein R^3 and X are as hereinbefore defined.

As another example, compounds of formula I wherein R^1, R^2, R^3, Z^1 and Z^2, are as hereinbefore defined, and Z^3 contains a -CS- moiety, are prepared from compounds of formula I wherein R^1, R^2, R^3, Z^1 and $Z^2$are as hereinbefore defined, and Z^3 contains a -CO- moiety, by reaction with

phosphorus pentasulfide or 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide, preferably in a solvent such as pyridine or toluene, and preferably at a temperature from about 0°C to reflux.

As another example, compounds of formula I wherein R^3 is as hereinbefore defined and contains an alkylsulfonyl, arylsulfonyl, alkylsulfinyl or arylsulfinyl group, R^1, R^2, Z, Z^1, Z^2 and Z^3 are as hereinbefore defined, are prepared by oxidising the corresponding compounds of formula I wherein R^3 is as hereinbefore defined and contains an alkylthio or arylthio group, R^1, R^2, Z, Z^1, Z^2 and Z^3 are as hereinbefore defined, preferably wherein Z, Z^1 and Z^2 each represent oxygen, and R^2 is alkyl or cycloalkyl, preferably with a peroxyacid, such as 3-chloroperbenzoic acid, preferably in an inert solvent, such as dichloromethane, preferably at about room temperature. Alternatively, the oxidation is carried out by reaction with a peroxomonosulfate, such as potassium peroxomonosulfate, conveniently in a solvent such as methanol, buffered to about pH 5, at temperatures from about 0°C to about room temperature. This latter method is preferred for compounds containing an acid-labile group, such as those wherein the moiety R^2 is unsaturated, such as a cyclopent-2-enyloxy group.

As another example, compounds of formula I wherein R^3 is as hereinbefore defined and contains a hydroxymethyl group, and R^1, R^2, Z, Z^1, Z^2 and Z^3 are as hereinbefore defined, are prepared by the reduction of the corresponding compounds of formula I wherein R^3 is as hereinbefore defined and contains an aryloxycarbonyl or, preferably, alkoxycarbonyl group, R^1, R^2, Z, Z^1, Z^2 and Z^3 are as hereinbefore defined, and Z is preferably oxygen, preferably by means of reacting an alkali metal borohydride, preferably in an inert solvent, such as tetrahydrofuran, preferably at about room temperature.

As another example, compounds of formula I wherein R^3 is as hereinbefore defined and contains a formyl group, and R^1, R^2, Z, Z^1, Z^2 and Z^3 are as hereinbefore defined, are prepared by the oxidising the corresponding compounds of formula I wherein R^3 is as hereinbefore defined and contains a hydroxymethyl group, R^1, R^2, Z, Z^1, Z^2 and Z^3 are as hereinbefore defined, and Z preferably being an oxygen atom, for example with oxalyl chloride and dimethyl sulfoxide, in a solvent such as dichloromethane, and preferably at a temperature lower than about -65°C, or,

preferably, by reaction with a complex of sulfur trioxide with an amine such as pyridine, preferably in the presence of an amine such as triethylamine, preferably at about room temperature.

As another example, compounds of formula I wherein R^3 is as hereinbefore defined and contains an amino group, and R^1, R^2, Z, Z^1, Z^2 and Z^3 are as hereinbefore defined, are prepared by the reducing the corresponding compounds of formula I wherein R^3 is as hereinbefore defined and contains a nitro group, R^1, R^2, Z, Z^1, Z^2 and Z^3 are as hereinbefore defined, and Z is preferably oxygen, preferably with iron in acidic conditions, such as in acetic acid, preferably at or above room temperature, more especially at the reflux temperature. Alternatively the reduction are carried out by reaction with hydrazine hydrate in the presence of ferric chloride and activated carbon, conveniently in a solvent such as methanol, at temperatures from about 25°C to about 80°C. This latter method is preferred for compounds containing an acid-labile group, such as those wherein the moiety R^2 is unsaturated, such as a cyclopent-2-enyloxy group.

As another example, compounds of formula I wherein R^3 is as hereinbefore defined and contains an alkanoylamino or aroylamino group, and R^1, R^2, Z, Z^1, Z^2 and Z^3 are as hereinbefore defined, are prepared from compounds of formula I wherein R^3 is as hereinbefore defined and contains an amino group, R^1, R^2, Z, Z^1, Z^2 and Z^3 are as hereinbefore defined, and Z is preferably oxygen, preferably by means of reaction with the appropriate acid halide or acid anhydride in the presence of a tertiary base, such as triethylamine, optionally in an inert solvent, and preferably at a temperature from about 0°C to reflux.

Compounds of formula I wherein R^3 is as hereinbefore described, including an azaheteroaryl group containing one or more nitrogen ring atoms, preferably imine (=N-), and R^1, R^2, Z, Z^1, Z^2 and Z^3 are as hereinbefore defined, may be converted to the corresponding compounds wherein a nitrogen atom of the azaheteroaryl moiety is oxidised to an N-oxide, R^1, R^2, Z, Z^1, Z^2 and Z^3 are hereinbefore defined, and preferably Z, Z^1 and Z^2 each represent oxygen, and R^2 is alkyl or cycloalkyl, preferably by reacting a peracid. for example peracetic acid in acetic acid or *m*-chloroperoxybenzoic acid in an inert solvent such as dichloromethane, at a temperature from about

room temperature to reflux, preferably at elevated temperature. Preferably wherein Z, Z^1 and Z^2 each represent oxygen, and R^2 is an oxidised cyclothioalkyl, such as cyclosulphinyl or sulphonyl, the reaction is carried out at a temperature from about room temperature to reflux, preferably at a reduced temperature. Alternatively, the oxidation is carried out by reaction with hydrogen peroxide in the presence of sodium tungstate at temperatures from about room temperature to about 60°C. This latter method is preferred for compounds containing an acid-labile group, such as those wherein the moiety R^2 contains a carbon-carbon double bond between its beta- and gamma-carbon atoms, such as a cyclopent-2-enyloxy group.

Compounds of formula I wherein R^3 represents an azaheteroaryl group containing a nitrogen ring atom as an N-oxide, and R^1, R^2, Z, Z^1, Z^2 and Z^3 are as hereinbefore defined, may be converted to the corresponding compounds wherein R^3 represents an azaheteroaryl group containing one or more nitrogen ring atoms, preferably imine (=N-), and R^1, R^2, Z, Z^1, Z^2 and Z^3 are hereinbefore defined, preferably by reacting in a deoxygenating system, for example diphosphorus tetraiodide in an inert solvent, such as dichloromethane, preferably at room temperature, or with a chlorotrialkylsilane, preferably chlorotrimethylsilane, in the presence of an alkali metal iodide, such as potassium iodide, and zinc, in an inert solvent, for example acetonitrile, at temperatures from about 0°C to about room temperature, preferably at reduced temperature.

For example, compounds of formula I wherein R^1 is as hereinbefore defined and is substituted by fluorine on a carbon atom thereof alpha to the attachment of R^1 to Z^1 as sulfur, or wherein R^2 is as hereinbefore defined and is substituted by fluorine on a carbon atom thereof alpha to the attachment of R^2 to Z^2 as sulfur, and R^3 and Z^3 as hereinbefore defined, are prepared by reacting xenon difluoride with corresponding compounds of formula I wherein said alpha-carbon atoms carry hydrogen atoms instead of said fluorine atoms. The reaction is conveniently carried out in a solvent, such as dichloromethane, in the presence of a molecular sieve, and in an inert atmosphere, at a low temperature, such as at about 0°C. Alternatively, compounds of formula I wherein R^1 is a difluoromethyl group may be prepared by reacting a compound of formula I or precursor wherein Z^1 is hydroxy or thiol with $HCBrF_2$ in the presence of a strong base in an inert solvent. Furthermore, compounds

of formula I wherein R^1 or R^2 is halo substituted may be prepared by reacting the corresponding compound of formula I wherein R^1 or R^2 is hydroxy substituted with diethylaminosulphur trifluoride (DAST) in an inert solvent such as methylene chloride.

The compounds of the present invention are useful in the form of the free base or acid or in the form of a pharmaceutically acceptable salt thereof. All forms are within the scope of the invention.

Where the compound of the present invention is substituted with a basic moiety, acid addition salts are formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free base form. The acids which can be used to prepare the acid addition salts include preferably those which produce, when combined with the free base, pharmaceutically acceptable salts, that is, salts whose anions are non-toxic to the patient in pharmaceutical doses of the salts, so that the beneficial inhibitory effects on TNF and PDE inherent in the free base are not vitiated by side effects ascribable to the anions. Although pharmaceutically acceptable salts of said basic compounds are preferred, all acid addition salts are useful as sources of the free base form even if the particular salt, per se, is desired only as an intermediate product as, for example, when the salt is formed only for purposes of purification, and identification, or when it is used as intermediate in preparing a pharmaceutically acceptable salt by ion exchange procedures. Pharmaceutically acceptable salts within the scope of the invention are those derived from the following acids: mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; and organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesufonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like. The corresponding acid addition salts comprise the following: hydrohalides, such as hydrochloride and hydrobromide, sulfate, phosphate, nitrate, sulfamate, acetate, citrate, lactate, tartarate, malonate, oxalate, salicylate, propionate, succinate, fumarate, maleate, methylene-bis-beta-hydroxynaphthoates, gentisates, mesylates, isethionates and di-p-toluoyltartratesmethanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and quinate, respectively.

According to a further feature of the invention, acid addition salts of the compounds of this invention are prepared by reaction of the free base with the appropriate acid, by the application or adaptation of known methods. For example, the acid addition salts of the compounds of this invention are prepared either by dissolving the free base in aqueous or aqueous-alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and acid in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The acid addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their acid addition salts by treatment with an alkali, such as aqueous sodium bicarbonate solution or aqueous ammonia solution.

Where the compound of the invention is substituted with an acidic moiety, base addition salts may be formed and are simply a more convenient form for use; and in practice, use of the salt form inherently amounts to use of the free acid form. The bases which can be used to prepare the base addition salts include preferably those which produce, when combined with the free acid, pharmaceutically acceptable salts, that is, salts whose cations are non-toxic to the animal organism in pharmaceutical doses of the salts, so that the beneficial inhibitory effects on TNF and PDE inherent in the free acid are not vitiated by side effects ascribable to the cations. Pharmaceutically acceptable salts, including for example alkali and alkaline earth metal salts, within the scope of the invention are those derived from the following bases: sodium hydride, sodium hydroxide, potassium hydroxide, calcium hydroxide, aluminum hydroxide, lithium hydroxide, magnesium hydroxide, zinc hydroxide, ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)-aminomethane, tetramethylammonium hydroxide, and the like.

Metal salts of compounds of the present invention may be obtained by contacting a hydride, hydroxide, carbonate or similar reactive compound of the

chosen metal in an aqueous or organic solvent with the free acid form of the compound. The aqueous solvent employed may be water or it may be a mixture of water with an organic solvent, preferably an alcohol such as methanol or ethanol, a ketone such as acetone, an aliphatic ether such as tetrahydrofuran, or an ester such as ethyl acetate. Such reactions are normally conducted at ambient temperature but they may, if desired, be conducted with heating.

Amine salts of compounds of the present invention may be obtained by contacting an amine in an aqueous or organic solvent with the free acid form of the compound. Suitable aqueous solvents include water and mixtures of water with alcohols such as methanol or ethanol, ethers such as tetrahydrofuran, nitriles such as acetonitrile, or ketones such as acetone. Amino acid salts may be similarly prepared.

The base addition salts of the compounds of this invention can be regenerated from the salts by the application or adaptation of known methods. For example, parent compounds of the invention can be regenerated from their base addition salts by treatment with an acid, such as hydrochloric acid.

As will be self-evident to those skilled in the art, some of the compounds of this invention do not form stable salts. However, acid addition salts are most likely to be formed by compounds of this invention wherein R^3 represents a nitrogen-containing heteroaryl group and/or wherein R^3 contains an amino group as a substituent. Preferable acid addition salts of the compounds of the invention are those wherein R^2 is other than an acid labile group.

As well as being useful in themselves as active compounds, salts of compounds of the invention are useful for the purposes of purification of the compounds, for example by exploitation of the solubility differences between the salts and the parent compounds, side products and/or starting materials by techniques well known to those skilled in the art.

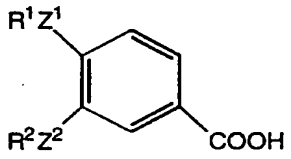
It will be apparent to those skilled in the art that certain compounds of formula I can exhibit isomerism, for example geometrical isomerism and optical isomerism. Optical isomers include compounds of the invention having asymmetric centers that may independently be in either the R or S

configuration. Geometrical isomers include the cis and trans forms of compounds of the invention having alkenyl moieties. Individual geometrical isomers, stereoisomers and mixtures thereof are within the scope of the present invention.

Such isomers can be separated from their mixtures, by the application or adaptation of known methods, for example chromatographic techniques and recrystallization techniques, or they are separately prepared from the appropriate isomers of their intermediates, for example by the application or adaptation of methods described herein.

The starting materials and intermediates are prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents.

For example, compounds of formula II above, wherein R^1, R^2, Z^1 and Z^2 are as hereinbefore defined, are prepared from compounds of formula XVI

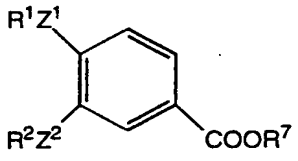


XVI

wherein R^1, R^2, Z^1 and Z^2 are as hereinbefore defined, by the application or adaptation of known methods for the preparation of acid halides from carboxylic acids. For example, when the moiety X in a compound of formula II represents a chloro, the reaction may be carried out by means of thionyl chloride or, preferably, oxalyl chloride in the presence of triethylamine, or as prepared by adaptation of the procedures described by K.R.Reistad *et al.*, Acta. Chemica. Scandanavica B, 28, 667-72 (1974), incorporated herein by reference.

Compounds of formula V above, wherein R^1, R^2, Z^1 and Z^2 are as hereinbefore defined, are prepared by reaction of the corresponding compounds of formula XVI above, wherein R^1, R^2, Z^1 and Z^2 are as hereinbefore defined, with ammonia, with the aid of an acid activating group, such as oxalyl chloride, from about 0°C to about room temperature.

Compounds of formula XVI above, wherein R^1, R^2, Z^1 and Z^2 are as hereinbefore defined, are prepared by hydrolysis of the corresponding compounds of formula XVII, wherein R^1, R^2, Z^1 and Z^2 are as hereinbefore

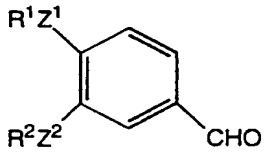


XVII

defined, R^2, Z^1 and Z^2 are as hereinbefore defined, and R^7 is alkyl, cycloalkyl or aralkyl containing up to 8 carbon atoms, by using potassium carbonate in water and an alcohol, such as methanol or ethanol, at a temperature between 50°C and 100°C.

Compounds of formula XI above, wherein R^1, R^2, R^5, R^6, Z, Z^1 and Z^2 are as hereinbefore defined, are prepared from the compounds of formula XVI above, wherein R^1, R^2, Z^1 and Z^2 are as hereinbefore defined, by reaction with HNR^4OR^5, wherein R^4 and R^5 are as hereinbefore defined, with the aid of an acid activating group, such as oxalyl chloride, in the presence of a tertiary amine, such as triethylamine, optionally in an inert solvent, for example dichloromethane.

Compounds of formula XVIII, wherein R^1, R^2, Z^1 and Z^2 are as



XVIII

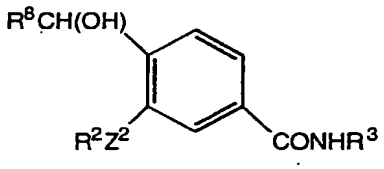
hereinbefore defined, are prepared from reduction of compounds of formula XIII above, wherein R^1, R^2, R^7, Z^1 and Z^2 are as hereinbefore defined, with diisobutylaluminium hydride in a solvent, such as diethyl ether, at low temperature, for instance -78°C to 0°C.

Compounds of formula X above, wherein R^1, R^2, R^3, Z^1 and Z^2 are as hereinbefore defined, are prepared by reaction of the compounds of formula

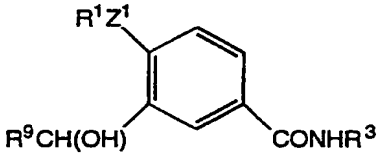
XVIII above, wherein R^1, R^2, Z^1 and Z^2 are as hereinbefore defined, with compounds of formula XV above, wherein R^3 is as hereinbefore defined. The reaction is conveniently carried out in a solvent, such as diethyl ether, at 0°C to 50°C.

Compounds of formula XIV above, wherein R^1, R^2, Z^1 and Z^2 are as hereinbefore defined, are prepared by dehydrating compounds of formula V above, wherein R^1, R^2, Z^1 and Z^2 are as hereinbefore defined, using chlorosulphonyl isocyanate, preferably in a solvent, such as dimethylformamide, preferably at temperatures between 0°C and room temperature.

Compounds of formulae XIX, wherein R^1, R^2, R^3, Z^1 and Z^2 are as

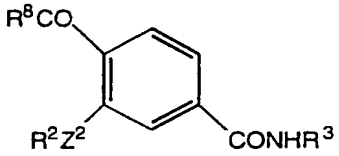


XIXa

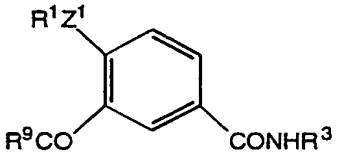


XIXb

hereinbefore defined, R^8 is alkyl containing up to about 3 carbon atoms, and R^9 is alkyl, alkynyl or alkenyl containing up to about 14, preferably up to 11, carbon atoms, are prepared by reducting of compounds of formulae XX,



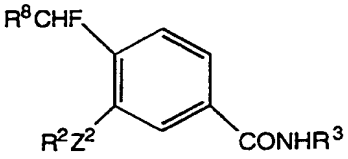
XXa



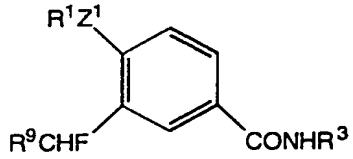
XXb

wherein R^1, R^2, R^3, R^8, R^9, Z^1 and Z^2 are as hereinbefore defined, using sodium borohydride in a solvent, such as ethanol, at between 0°C and room temperature.

Compounds of formulae (I'), wherein R^1, R^2, R^3, R^8, R^9, Z^1 and Z^2 are



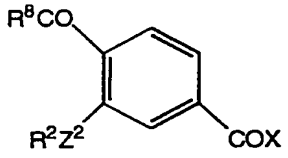
I'a



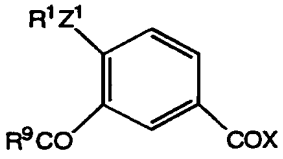
I'b

as hereinbefore defined, are prepared by the reaction of diethylaminosulphur trifluoride (DAST) with compounds of formulae XIX above, R^1, R^2, R^3, R^8, R^9, Z^1 and Z^2 as hereinbefore defined, in a solvent, such as dichloromethane, at low temperature e.g -78°C to -20°C.

Compounds of general formulae XX above, wherein R^1, R^2, R^8, R^9, Z^1 and Z^2 as hereinbefore defined, are prepared by reaction of the corresponding compounds of formulae XXI, wherein R^1, R^2, R^8, R^9, Z^1, Z^2 and X are as



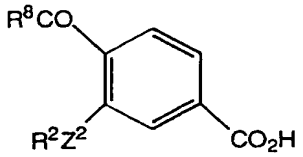
XXIa



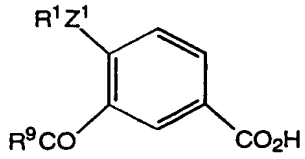
XXIb

hereinbefore defined, with compounds of the formula III above, as hereinbefore defined, in the presence of a base such as an alkali metal hydride, such as sodium hydride, or an amine, preferably a tertiary amine, such as triethylamine or pyridine, optionally in an inert solvent, for example dichloromethane, dimethylformamide, or an ether, such as diethyl ether or tetrahydrofuran, preferably at a temperature from about 0°C to the reflux temperature or at the melting point of the reaction mixture..

Compounds of formulae XXI above, wherein R^1, R^2, R^8, R^9, Z^1, Z^2 and X are as hereinbefore defined, are prepared by reaction of compounds of formulae XXII, wherein R^1, R^2, R^8, R^9, Z^1 and Z^2 are as hereinbefore



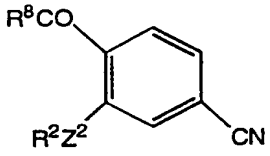
XXIIa



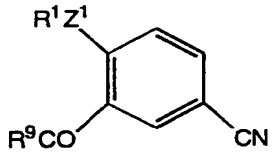
XXIIb

defined, by application or adaptation of known methods for the preparation of acid halides and mixed acid anhydrides.

Compounds of formulae XXII, above , wherein R^1, R^2, R^8, R^9, Z^1 and Z^2 are as hereinbefore defined, are prepared from compounds of formulae XXIII, wherein R^1, R^2, R^8, R^9, Z^1 and Z^2 are as hereinbefore defined, defined,



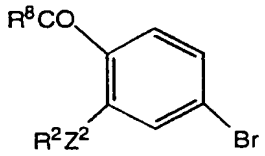
XXIIIa



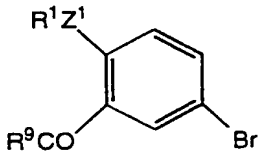
XXIIIb

using a base, such as potassium hydroxide, preferably in a solvent, such as ethylene glycol, at temperatures between 100°C and 180°C.

Compounds of formulae XXIII above, wherein R^1, R^2, R^8, R^9, Z^1 and Z^2 are as hereinbefore defined, are prepared from corresponding compounds of the formulae XXIV, wherein R^1, R^2, R^8, R^9, Z^1 and Z^2 are as hereinbefore



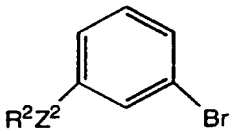
XXIVa



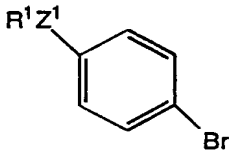
XXIVb

defined, using copper (I) cyanide and copper (II) sulphate, preferably in a solvent, such as dimethylformamide, at temperatures between 150°C and 200°C.

Compounds of formulae XXIV above, wherein R^1, R^2, R^8, R^9, Z^1 and Z^2 are as hereinbefore defined, are prepared by reacting compounds of the formulae XXVa and XXVb, wherein R^1, R^2, Z^1 and Z^2 are as hereinbefore



XXVa



XXVb

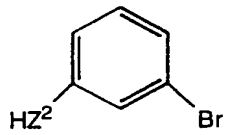
defined, with compounds of formulae XXVIa and XXVIb respectively, wherein

R^8COCl R^9COCl

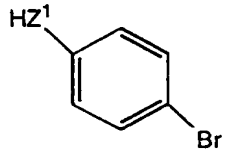
XXVIa XXVIb

R^8 and R^9 are as defined hereinbefore, in the presence of a Lewis acid catalyst, such as aluminium chloride, preferably in a solvent such as nitrobenzene, at temperatures between room temperature and 200°C.

Compounds of formulae XXV above, wherein R^1, R^2, Z^1 and Z^2 are as hereinbefore defined, are prepared by alkylating compounds of formulae XXVII, wherein Z^1 and Z^2 are as hereinbefore defined, with compounds of



XXVIIa



XXVIIb

formulae VIII and XXVIII, wherein R^1, R^2, and X are as hereinbefore defined,

R^2X R^1X

VIII XXVIII

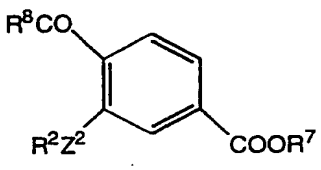
with the aid of a metal hydride, such as sodium hydride, or base, such as potassium carbonate, preferably in a solvent, such as dimethylformamide, between room temperature and 100°C. Alternatively, the reaction is carried out by reacting compounds of formulae XVII above, wherein R^1 and R^2 are as hereinbefore defined, and , Z^1 and Z^2 are oxygen, with compounds of formulae IX and XXIX respectively in the presence of triphenylphosphine and

R^2OH R^1OH

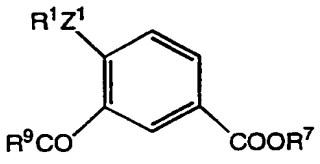
IX XXIX

diisopropylazodicarboxylate, optionally in a solvent, such as toluene, at temperatures between 0°C and 80°C.

Compounds of formula XXXX, wherein R^1, R^2, R^7, R^8, R^9, Z^1 and Z^2 are



XXXXa



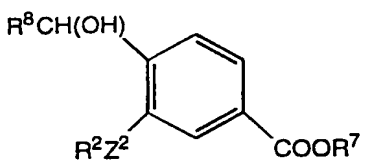
XXXXb

as hereinbefore defined, by esterifying compounds of formulae XXII above, wherein R^1, R^2, R^8, R^9, Z^1 and Z^2 are as hereinbefore defined, with compounds of formula XXXXI, wherein R^7 is as hereinbefore defined,

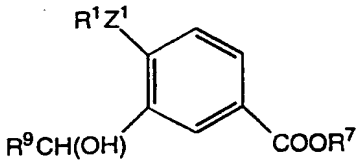
R^7OH XXXXI

in the presence of a trace of acid, such as concentrated sulphuric acid, optionally in an inert solvent, such as toluene, at temperatures between room temperature and 100°C.

Compounds of formulae XXXXII, wherein R^1, R^2, R^7, R^8, R^9, Z^1 and Z^2



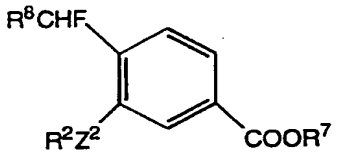
XXXXIIa



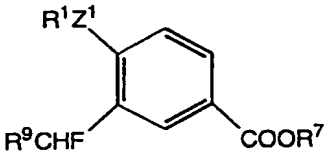
XXXXIIb

are as hereinbefore defined, are prepared by reducting of compounds of formulae XXXX above, wherein R^1, R^2, R^7, R^8, R^9, Z^1 and Z^2 are as hereinbefore defined, using sodium borohydride in a solvent, such as ethanol, at between 0°C and room temperature.

Compounds of general formulae XVII', wherein R^1, R^2, R^7, R^8, R^9, Z^1



XVII'a



XXVII'b

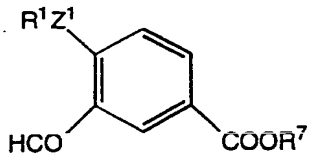
and Z^2 are as hereinbefore defined, are prepared by the reaction of diethylaminosulphur trifluoride with compounds of formulae XXXXII, wherein R^1, R^2, R^7, R^8, R^9, Z^1 and Z^2 are as hereinbefore defined, in a solvent, such as dichloromethane, at low temperature e.g -78°C to -20°C.

Compounds of general formula (I) above, wherein R^1, R^2, R^3, Z^1 and Z^2 are as hereinbefore defined, are prepared by reduction of compounds of formulae XX above, wherein R^1, R^2, R^3, R^8, R^9, Z^1 and Z^2 are as hereinbefore defined, using a silane, such as triethylsilane in the presence of a strong acid, such as trifluoroacetic acid, optionally in an inert solvent, such as dichloromethane, at temperatures between 0°C and room temperature.

Compounds of formula XVII above, wherein R^1, R^2, R^7, Z^1 and Z^2, are prepared by the reducing compounds of formulae XXXX above, wherein R^1, R^2, R^7, R^8, R^9, Z^1 and Z^2 are as hereinbefore defined, using a silane, such as triethylsilane in the presence of a strong acid, such as trifluoroacetic acid,

optionally in an inert solvent, such as dichloromethane, at temperatures between 0°C and room temperature.

Compounds of formula IX above, wherein R^2 is alkenyl, R^1, R^7 and Z^1 are as hereinbefore defined, and Z^2 is a direct bond, are prepared from compounds of formula XXXXIII, wherein R^1, R^7 and Z^1 are as hereinbefore



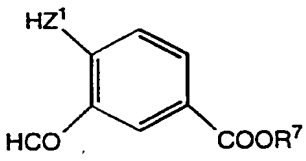
XXXXIII

defined, with compounds of formula XXXXIV, wherein R^{10} represents

$$R^{10}CH_2PPh_3X \qquad \text{XXXXIV}$$

alkyl, alkenyl or alkynyl group containing up to about 13, preferably up to 10, carbon atoms, X is as hereinbefore defined, and Ph represents phenyl, in the presence of a base, such as butyllithium, preferably in a solvent, such as tetrahydrofuran, preferably below about 5°C.

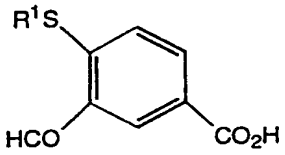
Compounds of general formula XXXXIII, wherein R^1, R^7 and Z^1 are as hereinbefore defined, are prepared from compounds of the formula XXXXV,



XXXXV

wherein R^7 and Z^1 are as hereinbefore defined, by reaction with compoundsof formula XXVIII, wherein R^1 and X are as hereinbefore defined, with the aid of a metal hydride, such as sodium hydride, or base, such as potassium carbonate, preferably in a solvent, such as dimethylformamide, between room temperature and 100°C.

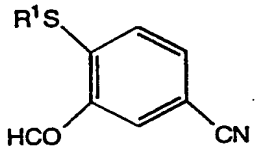
Compounds of general formula XXXXV, wherein R^1 and R^7 are as hereinbefore defined, and Z^1 is a S atom, are prepared from esterification of compounds of the formula XXXXVI, wherein R^1 is as hereinbefore defined, with



XXXXVI

compounds of formula XXXXI above, wherein R^7 is as hereinbefore defined, in the presence of a trace of acid, such as concentrated sulphuric acid, optionally in an inert solvent, such as toluene, at temperatures between room temperature and 100°C.

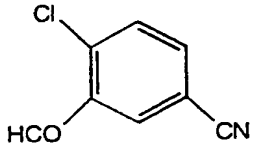
Compounds of formula XXXXVI, wherein R^1 is as hereinbefore defined, are prepared from compounds of the formula XXXXVII, wherein R^1 is as



XXXXVII

hereinbefore defined, using a base, such as potassium hydroxide, preferably in a solvent, such as ethylene glycol, at temperatures between 100°C and 180°C.

Compounds of formula XXXXVII above, wherein R^1 is as hereinbefore defined, are prepared from compound XXXXVIII, by reaction with compounds



XXXXVIII

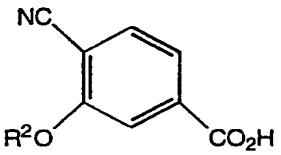
of formula XXXXIX, wherein R^1 and Z^1 are as hereinbefore defined, with the aid

R^1Z^1H XXXXIX

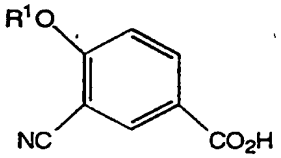
of a metal hydride, such as sodium hydride, or base, such as potassium carbonate, preferably in a solvent, such as dimethylformamide, between room temperature and 100°C.

Compounds of formula (I), wherein R^1 is a group as hereinbefore defined, Z^1 is a oxygen or sulphur atom, R^2 is a group as hereinbefore defined, Z^2 is a bond , Z^3 represents a CONH or COCH2 linkage, the other symbols being as hereinbefore defined, are prepared by hydrogenation of the corresponding compounds of formula (I) wherein Z^2 is a direct bond and R^2 contains a unsaturated moiety. The reaction is conveniently carried out using hydrogen in the presence of a catalyst, such as palladium on carbon, preferably in a solvent, such as ethanol, at about room temperature.

Alternatively, compounds of formulae XXII, wherein R^1, R^2, R^8 and R^9 are as hereinbefore defined, are prepared by reacting compounds of formulae XXXXX, wherein R^1 and R^2 are as hereinbefore defined, with compounds



XXXXXa



XXXXXb

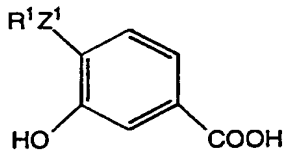
of formulae XXXXXIa and XXXXXIb respectively, wherein

R^8MgX R^9MgX

XXXXXIa XXXXXIb

R^8 and R^9 are as defined hereinbefore, in the presence of cuprous bromide in an inert solvent, such as tetrahydrofuran, at temperatures from room temperature to 80°C.

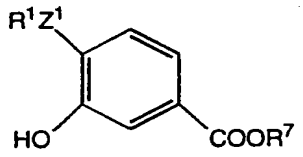
Compounds of formula XVI above, wherein R^1 and R^2 are ethyl or methyl, Z^1 is a direct bond, Z^2 is oxygen, and R^2 is as hereinbefore defined, are prepared by alkylating compounds of formula XXXXXII, wherein R^1 is as



XXXXXII

hereinbefore defined, and Z^1 is a direct bond, with corresponding compounds of formula VIII, wherein R^2 and X are as hereinbefore defined, using a metal hydride, such as sodium hydride, or base, such as potassium carbonate, preferably in a solvent, such as dimethylformamide, between room temperature and 100°C.

Compounds of formula XIII, wherein R^1 and R^2 are ethyl or methyl, Z^1 is a direct bond, Z^2 is oxygen, and R^2 and R^7 as hereinbefore defined, are prepared from corresponding compounds of formula XXXXXIII, wherein R^1 and



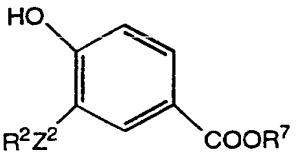
XXXXXIII

R^7 are as hereinbefore defined, and Z^1 is a direct bond, with corresponding compounds of formula VIII above, wherein R^2 and X are as hereinbefore defined, using a metal hydride, such as sodium hydride, preferably in a solvent, such as dimethylformamide, between room temperature and 100°C. Alternatively the reaction is carried out using compounds of formula IX above, wherein R^2 is as hereinbefore defined, in the presence of triphenylphosphine and diisopropyl azodicarboxylate, optionally in a solvent, such as toluene, at temperatures between 0°C and 80°C.

Compounds of formula XXXXXIII, wherein R^1 and R^7 are as hereinbefore defined, and Z^1 is a direct bond, are prepared by esterification of the compounds of formula XXXXXII, wherein R^1 is as hereinbefore defined,

and Z^1 is a direct bond, with compounds of formula XXXXI, wherein R^7 is as hereinbefore defined, in the presence of a trace of acid, such as concentrated sulphuric acid, optionally in an inert solvent, such as toluene, at temperatures between room temperature and 100°C.

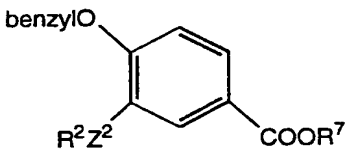
Compounds of formula XIII above, wherein R^1, R^2 and R^7 are as hereinbefore defined, Z^1 is oxygen, Z^2 is a direct bond, are prepared from the corresponding compounds of the formula XXXXXIV, wherein R^2 and



XXXXXIV

R^7 are as hereinbefore defined, and Z^2 is a direct bond, by reaction with corresponding compounds of formula XXVIII, wherein R^1 and X are as hereinbefore defined, with a metal hydride, such as sodium hydride, or base, such as potassium carbonate, preferably in a solvent, such as dimethylformamide, between room temperature and 100°C.

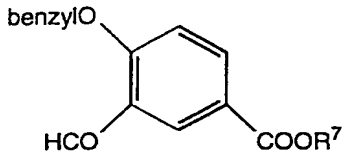
Compounds of formula XXXXXIV, wherein R^2 and R^7 are as hereinbefore defined, and Z^2 is a direct bond, are prepared by hydrogenation of the compounds of the formula XXXXXV, wherein R^7 is as hereinbefore



XXXXXV

defined, Z^2 is a direct bond, and R^2 contains an unsaturated moiety, by using hydrogen in the presence of a catalyst, such as palladium on carbon, preferably in a solvent, such as ethanol.

Compounds of formula XXXXXV above, wherein R^7 is as hereinbefore defined, Z^2 is a direct bond, and R^2 contains an unsaturated moiety, are prepared from the reaction of compounds of formula XXXXXVI, wherein R^7 is



XXXXXVI

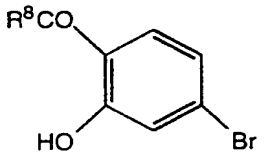
as hereinbefore defined, with compounds of formula XXXXIV above, , wherein R^{10} represents

$$R^{10}CH_2PPh_3X \qquad XXXXIV$$

alkyl, alkenyl or alkynyl group containing up to about 13, preferably up to 10, carbon atoms, X is as hereinbefore defined, and Ph represents phenyl, in the presence of a base, such as butyllithium, preferably in the presence of a solvent, such as tetrahydrofuran, preferably below 5°C.

Compounds of formula XXXXXVI above, wherein R^7 is as hereinbefore defined, are prepared from compounds of the formula XXXXV, wherein R^7 and Z^1 are as hereinbefore defined, by reaction with benzyl bromide, with the aid of a metal hydride, such as sodium hydride, or base, such as potassium carbonate, preferably in a solent, such as dimethylformamide, between room temperature and 100°C.

Alternatively, compounds of formula XXIVa, wherein R^2 and R^8 are as hereinbefore defined, and Z^2 is oxygen, are prepared from alkylation of compounds of formula XXXXXVII, wherein R^8 is as

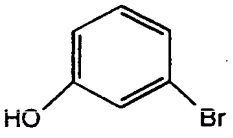


XXXXXVII

hereinbefore defined, with the corresponding compounds of formulae VIII above, wherein R^2 and X are as hereinbefore defined, with the aid of a base, such as potassium carbonate, preferably in a solvent, such as dimethylformamide, between room temperature and 100°C. Alternatively the reaction is carried out using compounds of the formula IX above, wherein R^2 is

as hereinbefore defined, in the presence of triphenylphosphine and diisopropylazodicarboxylate, optionally in a solvent, such as toluene, at temperatures between 0°C and 80°C.

Compounds of formula XXXXXVII above, wherein R^8 is as hereinbefore defined, are prepared from reaction of compound of formula XXXXXVIII,



XXXXXVIII,

with corresponding compounds of formula XXVIa above, wherein R^8 is as hereinbefore defined, in the presence of a Lewis acid catalyst, such as aluminiun chloride, preferably in a solvent such as nitrobenzene, at temperatures betweeen room temperature and 200°C.

The following Examples illustrate the preparation of the compounds according to the invention and the Reference Examples illustrate the preparation of the intermediates.

EXAMPLE 1 Compound A

A stirred suspension of N-(3,5-dichloropyrid-4-yl)-3-cyclopentanecarbonyl-4-methoxybenzamide (1.97 g) (prepared as described in Reference Example 2) in dry dichloromethane (ethanol-free; 9.9 mL), under nitrogen, is slowly treated with trifluoroacetic acid (2.85 g) during 5 minutes at 5-10°C. The resulting pale yellow solution is allowed to warm to 25°C during 20 minutes, then stirred at this temperature during treatment with triethylsilane (1.28 g) during 10 minutes and for 4 hours 30 minutes thereafter. After standing for a further 3 days, the solution is diluted with dichloromethane (50 mL), washed successively with water (2 x 10 mL), saturated aqueous sodium hydrogen carbonate solution (2 x 10 mL) and water (2 x 10 mL), dried over anhydrous magnesium sulphate and the solvent removed in vacuo. The residual oil is washed with pentane (50 mL) by decantation, and subjected to flash chromatography on silica gel, using a mixture of ethyl acetate and cyclohexane (1:3v/v), as eluent, followed by crystallisation from a mixture of

tert-butyl methyl ether and diisopropyl ether (1:1v/v), to give N-(3,5-dichloropyrid-4-yl)-3-cyclopentylmethyl-4-methoxybenzamide (1.16 g) in the form of colourless needles, m.p. 110°C and 134°C. [Elemental analysis:- C,59.8;H,5.23;N,7.3%; Calculated:- C,60.17;H,5.31; N,7.39%].

EXAMPLE 2

Sodium hydride (0.36 g) is added portionwise to a stirred solution of 4-amino-3,5-dichloropyridine (0.892 g) in dry dimethylformamide (25 mL) at room temperature and the mixture is stirred under an atmosphere of nitrogen for 20 minutes. A solution of 3-cyclopentyloxy-4-ethylbenzoyl chloride (1.04 g) (prepared as described in Reference Example 3) in dry dimethylformamide (8 mL) is added dropwise and the reaction mixture is stirred at room temperature for 2 hours and at 60°C for 90 minutes. Dimethylformamide is evaporated off under reduced pressure, water (90 mL) is added and the mixture is extracted with ethyl acetate (2 x 90 mL). The combined organic extracts are dried over magnesium sulphate, evaporated under reduced pressure and subjected to mplc, eluting with a mixture of diethyl ether and pentane (3:7v/v), to give N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-ethylbenzamide in the form of a white solid (0.93 g),m.p. 122-123°C. [Elemental analysis:- C,60.3;H,5.37;N,7.4%; calculated:- C,60.16;H,5.33; N,7.39%].

EXAMPLE 3

By proceeding in a similar manner to that described in Example 2, but using the appropriate quantity of 3-cyclopentyloxy-4-methylbenzoyl chloride (prepared as described in Reference Example 4), there is prepared N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-methylbenzamide in the form of a white solid, m.p. 136-138°C. [Elemental analysis:- C,58.9; H,4.97;N,7.6;Cl,19.4%; calculated:- C,59.19;H,4.96; N,7.67;Cl,19.41%].

EXAMPLE 4

Hydrogen peroxide (3.5 mL) is added to a stirred suspension of N-(3,5-dichloropyrid-4-yl) 3-cyclopentylmethyl-4-methoxybenzamide (0.47 g, prepared as described in Example 1) in glacial acetic acid (10 mL). The

mixture is stirred at 70-80 °C for 4 hours. After cooling, the mixture is basified by treatment with aqueous sodium hydroxide (2 M), and extracted with ethyl acetate (100 mL). The extracts are washed with brine, dried over sodium sulphate and evaporated. The resulting residue is purified by flash chromatography on silica gel, using a mixture of methanol and dichloromethane (1:99 to 2:98 v/v) to give a white solid, which is triturated with ether/pentane to give N-(3,5-dichloro-1-oxido-4-pyridinio) 3-cyclopentylmethyl-4-methoxybenzamide (0.11 g) in the form of a white solid, m.p. 125-129 °C. [Elemental analysis:- C,57.40; H,5.24; N,6.80 %; calculated:- C,57.73; H,5.10; N,7.09 %].

EXAMPLE 5

By proceeding in a similar manner to that described in Example 2, but using the appropriate quantity of 3-(exo)-8,9,10-trinorbornyl-2-oxy-4-ethylbenzoyl chloride (prepared as described in Reference Example10), there is prepared N-(3,5-dichloropyrid-4-yl)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-ethylbenzamide in the form of a white foam. [Elemental analysis:-C,62.30; H,5.63; N,6.50 %; calculated:- C,62.23; H,5.47; N,6.90 %].

EXAMPLE 6

By proceeding in a similar manner to that described in Example 2, but using the appropriate quantity of 3-cyclopentylidenemethyl-4-methoxybenzoyl chloride (prepared as described in Reference Example 13), there is prepared N-(3,5-dichloropyrid-4-yl)-3-cyclopentylidenemethyl-4-methoxybenzamide in the form of a white solid, m.p. 155-156°C. [Elemental analysis:- C,60.40; H,4.77; N,7.40 %; calculated:- C,60.48; H,4.80; N,7.42 %].

EXAMPLE 7

By proceeding in a similar manner to that described in Example 2, but using the appropriate quantity of 3-(2-methylpropenyl)-4-methoxybenzoyl chloride (prepared as described in Reference Example 16), there is prepared N-(3,5-dichloropyrid-4-yl)-3-(2-methylpropenyl)-4-methoxybenzamide in the form of a white solid, m.p. 154-155°C. [Elemental analysis:- C,58.40; H,4.68; N,7.90 %; calculated:- C,58.13; H,4.59; N,7.97 %.]

EXAMPLE 8

By proceeding in a similar manner to that described in Example 2, but using the appropriate quantity of 3-cyclopentylidenemethyl-4-difluoromethoxybenzoyl chloride (prepared as described in Reference Example 22), there is prepared N-(3,5-dichloropyrid-4-yl)-3-cyclopentylidenemethyl-4-difluoromethoxybenzamide in the form of a white solid, m.p. 122-123°C. [Elemental analysis:- C,54.60; H,4.31; N,6.76 %; calculated:- C,54.96; H,4.31; N,6.75 %].

EXAMPLE 9

N-(3,5-dichloropyrid-4-yl)-3-cyclopentylhydroxymethyl-4-methoxybenzamide (0.3 g, prepared as described in Reference Example 23) in dry dichloromethane (5 mL) is added dropwise to a solution of diethylaminosulphur trifluoride (0.12 g) in dry dichloromethane (5 mL) at -78°C. Stirring at this temperature is continued for a further 25 minutes before the reaction is quenched with water (15 mL). After allowing the mixture to warm up to room temperature the layers are separated, the aqueous layer is further extracted with dichloromethane (20 mL) and the combined organic extracts washed with saturated aqueous sodium hydrogen carbonate (25 mL), dried over magnesium sulphate and evaporated. The resulting residue is purified by flash chromatography on silica gel, using a mixture of ethyl acetate and pentane (1:2 v/v) to give N-(3,5-dichloropyrid-4-yl)-3-cyclopentylfluoromethyl-4-methoxybenzamide (0.1 g) in the form of a white solid, m.p. 73-75°C. [Elemental analysis:- C,57.50; H,5.06; N,6.69 %; calculated:- C,57.43; H,4.82; N,7.05 %].

EXAMPLE 10

By proceeding in a similar manner to that described in Example 9, but using the appropriate quantity of N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-(1-hydroxyethyl)benzamide (0.3 g, prepared as described in Reference Example 29), there is prepared N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-(1-fluoroethyl)benzamide, in the form of a white solid, m.p. 141-143°C.

[Elemental analysis:- C,57.50; H,4.85; N,7.10 %; calculated:- C,57.44; H,4.82; N,7.05 %].

REFERENCE EXAMPLE 1

A stirred suspension of 3-cyano-4-methoxybenzoic acid (14.2 g) (prepared as describe in Eur. Pat. Appl. EP 279698) in dry tetrahydrofuran (142 mL) and under an atmosphere of nitrogen is treated with a solution of cyclopentyl magnesium chloride in tetrahydrofuran (126 mL; 1.4 M) during 10 minutes at 25°C. Cuprous bromide (0.4 g) is added to the orange-red solution, the mixture is heated and stirred at reflux for 6 hours, and then it is poured into a mixture of ice-water (670 mL) and aqueous hydrochloric acid (400 mL; 1 M). The crude product is extracted with ethyl acetate (1 x 400, 2 x 200 mL) and the combined extracts are washed successively with water (2 x 120 mL) and saturated aqueous sodium chloride solution (2 x 80 mL). After drying over anhydrous magnesium sulphate the extracts are concentrated in vacuo and cooled to 25°C to give the product in the form of an off-white crystalline solid. A further quantity of this substance is obtained from the mother liquor by evaporation in vacuo and flash chromatography of the residue over silica gel, using as eluent a mixture of ethyl acetate and cyclohexane (1:2v/v), followed by purification of the material thus obtained by sequential treatment with diisopropyl ether and ethyl acetate. The combined crops (9.8 g) of 3-cyclopentanecarbonyl-4-methoxybenzoic acid have a melting point of 184-186°C. [Elemental analysis:- C,67.2;H,6.45%; calculated:- C,67.73;H,6.50%. NMR ($CDCl_3$):- 1.55-1.75(m;4H),1.82-1.90(m;4H),3.60-3.69(p;1H),3.95-3.98(s;3H), 7.00-7.03(d;1H),8.17-8.21(dd;1H),8.26-8.28(d;1H)].

REFERENCE EXAMPLE 2

A stirred solution/suspension of 3-cyclo-pentanecarbonyl-4-methoxybenzoic acid (11.4 g) (prepared as described in Reference Example 1) in dry tetrahydrofuran (77 mL) and under an atmosphere of nitrogen is treated with ethyl chloromethanoate (5.48 g) during 5 minutes at 17-20°C. The temperature is allowed to rise to 25°C and maintained at this temperature for 30 minutes. The resulting amber solution is then treated with dry triethylamine (5.11 g) during 10 minutes, and stirred for a further 1 hour. The suspension

formed is filtered rapidly through a dry bed of diatomaceous earth and the filtrate is concentrated in vacuo to a volume of 50 mL, to give "solution A" containing 3-cyclopentane-carbonyl-4-methoxybenzoic formic anhydride.

A stirred solution of 4-amino-3,5-dichloropyridine (8.23 g) in dry tetrahydrofuran, under nitrogen, is treated with a 60% dispersion of sodium hydride in oil (4.04 g; containing 2.47 g of sodium hydride) in portions during 15 minutes at 25°C. The suspension obtained is stirred at this temperature for 1 hour. The stirred suspension is then treated with solution A during 10 minutes and then it is stirred for 30 minutes thereafter. After standing for a further 20 hours, the solution obtained is added to aqueous potassium carbonate solution (690 mL; 5%w/v) with cooling and stirring. It is then extracted with ethyl acetate (3 x 200 mL) and the combined extracts are washed successively with water (2 x 50 mL), aqueous hydrochloric acid (2 x 50 mL; 1M), water (2 x 50 mL) and saturated aqueous sodium chloride solution (2 x 50 mL). The solution is dried using anhydrous magnesium sulphate, the solvent is evaporated in vacuo, and the residual solid is treated with tert-butyl methyl ether (200 mL), heated at reflux for 10 minutes, cooled and filtered, to give N-(3,5-dichloropyrid-4-yl)-3-cyclopentanecarbonyl-4-methoxybenzamide in the form of an off-white crystalline solid (8.5 g), m.p. 180-182°C. [Elemental analysis:- C,58.0;H,4.56;N,7.0%. calculated:- C,58.03;H,4.61; N,7.12%].

REFERENCE EXAMPLE 3

Thionyl chloride (1.1 mL) is added to a solution of 3-cyclopentyloxy-4-ethylbenzoic acid (1.07 g) (prepared as described in Reference Example 5) in toluene (7 mL) and the mixture is heated at 80°C for 3 hours. Evaporation under reduced pressure gives 3-cyclopentyloxy-4-ethylbenzoyl chloride (1 g), in the form of a pale brown oil which is used without further purification.

REFERENCE EXAMPLE 4

By proceeding in a similar manner to that described in Reference Example 3, but using the appropriate quantity of 3-cyclopentyloxy-4-methylbenzoic acid (prepared as described in Reference Example 6), there is

prepared 3-cyclopentyloxy-4-methylbenzoyl chloride, in the form of a brown oil which is used without further purification.

REFERENCE EXAMPLE 5

Sodium hydride (1.6 g of 60% dispersion in mineral oil; 40 mmol) is added portionwise to a solution of 4-ethyl-3-hydroxybenzoic acid (3.32 g) (prepared as described in D. S. Noyce and L. J. Dolby, J. Org. Chem. 26, 1732 (1961) in dry dimethyl-formamide and the mixture is stirred at room temperature for 15 minutes. Cyclopentyl bromide (2.98 g) is added and the mixture is heated at 60°C for 3 hours. Dimethylformamide is evaporated off under reduced pressure, and the dark residue is dissolved in water (100 mL), acidified by treatment with concentrated hydrochloric acid and extracted with dichloromethane (2 x 100 mL). The combined organic extracts are dried over magnesium sulphate, evaporated under reduced pressure and subjected to mplc, eluting with a mixture of ethyl acetate and pentane, to give 3-cyclopentyloxy-4-ethylbenzoic acid (1.1 g), in the form of a pale yellow solid, m.p. 101°C. [NMR ($CDCl_3$):- 7.63(dd,1H,J=8Hz,2Hz); 7.52(d,1H,J=2Hz), 7.22(d,1H,J=8Hz),4.87(m,1H);2.65(q,2H,J=8Hz),2.0-1.6(m,8H); 1.19(t,3H,J=8Hz)].

REFERENCE EXAMPLE 6

By proceeding in a similar manner to that described in Reference Example 5, but using the appropriate quantity of 3-hydroxy-4-methylbenzoic acid (prepared as described in D. S. Noyce and L. J. Dolby, J. Org. Chem. 26, 1732 (1961), there is prepared 3-cyclopentyloxy-4-methylbenzoic acid, m.p. 152-154°C. [NMR ($CDCl_3$):- 7.6(dd,1H,J=8Hzm,2Hz); 7.53(d,1H,J=2Hz), 7.4(d,1H,J=8Hz),4.85(m,1H);2.25(s,3H),2.0-1.6(m,8H)].

REFERENCE EXAMPLE 7

To a solution of 4-ethyl-3-hydroxybenzoic acid in methanol (300 mL) is added concentrated sulphuric acid. The resulting mixture is left to stand for 2 days at room temperature, then heated to reflux for 45 minutes. After cooling, the solvent is evaporated and the residue partitioned between diethyl ether (200 mL) and water (200 mL), the layers throughly shaken, separated and the

aqueous layer further extracted with diethyl ether (2 x 100 mL). The combined organic extracts are dried over magnesium sulphate and solvent evaporated. The resulting residue is purified by flash chromatography on silica gel eluting with a mixture of ethyl acetate and pentane (1:3 v/v) to give methyl 4-ethyl-3-hydroxybenzoate (4.4 g) in the form of an off white solid, m.p. 62-63°C.

REFERENCE EXAMPLE 8

A solution of triphenylphosphine (1.45 g) in dry tetrahydrofuran (20 mL) is treated with a solution of diisopropyl azodicarboxylate (1.12 g) in dry tetrahydrofuran (4 mL). The resulting creamy precipitate is stirred at room temperature for 30 minutes, then cooled to below 5°C and treated dropwise with a solution of endo-8,9,10-trinorborneol (0.68 g) and methyl 4-ethyl-3-hydroxybenzoate (1 g, prepared as described in Reference Example 7) in dry tetrahydrofuran (40 mL), maintaining the temperature below 5°C. The resulting mixture is then allowed to warm to room temperature and then heated at reflux for 15 hours, cooled, poured in to water (100 mL) and extracted with ethyl acetate (2 x 75 mL). The combined organic extracts are dried over magnesium sulphate, solvent evaporated, and the residue purified by flash chromatography on silica gel eluting with a mixture of ethyl acetate and pentane (1:20 v/v) to give methyl 3-(exo)-8,9,10-trinorbornyl-2-oxy-4-ethylbenzoate (0.95 g) in the form of a colourless oil.

REFERENCE EXAMPLE 9

A stirred refluxing solution of methyl 3-(exo)-8,9,10-trinorbornyl-2-oxy-4-ethylbenzoate (0.9 g, prepared as described in Reference Example 8) in methanol (30 mL) is treated with a solution of potassium carbonate (0.58 g) in water (15 mL). The resulting suspension is heated at reflux for 24 hours, allowed to cool to room temperature and the methanol is then removed under reduced pressure. The aqueous residue is acidified to pH 1 with 1 M hydrochloric acid and extracted with dichloromethane (3 x 50 mL). The combined organic extracts are dried over magnesium sulphate and the solvent removed to give 3-(exo)-8,9,10-trinorbornyl-2-oxy-4-ethylbenzoic acid (0.8 g) in the form of a white solid, m.p. 110°C, which is used without further purification.

REFERENCE EXAMPLE 10

By proceeding in a similar manner to that described in Reference Example 3, but using the appropriate quantity of 3-(exo)-8,9,10-trinorbornyl-2-oxy-4-ethylbenzoic acid (prepared as described in Reference Example 9), there is prepared 3-(exo)-8,9,10-trinorbornyl-2-oxy-4-ethylbenzoyl chloride in the form of a brown oil, which is used without further purification.

REFERENCE EXAMPLE 11

A solution of cyclopentyltriphenylphosphonium bromide (6.68 g) in dry tetrahydrofuran (100 mL) under nitrogen is cooled to below -70°C. To this is added *n*-butyl lithium (2.5 M, 5.6 mL) dropwise keeping the temperature below -70°C. Once addition is complete the mixture is allowed to warm to room temperature and further stirred at this temperature for 1 hour, before recooling to below -70°C and the addition of methyl 3-formyl-4-methoxybenzoate (3.2 g) (prepared as described in WO 9217449) in dry tetrahydrofuran (60 mL) dropwise over 45 minutes, keeping the temperature below -60°C. The mixture is then stirred below -60°C for 10 minutes, before allowing to warm to room temperature and stirring for a further 30 minutes. The mixture is then quenched with water (50 mL), the layers separated and the aqueous layer further extracted with ethyl acetate (3 x 20 mL). The combined organic extracts are dried over magnesium sulphate and evaporated. The resulting residue is purified by flash chromatography on silica gel, using a mixture of ethyl acetate and pentane (2:3 v/v) to give methyl 3-cyclopentylidenemethyl-4-methoxybenzoate (1.23 g) in the form of an off white solid, m.p. 55-57°C.

REFERENCE EXAMPLE 12

By proceeding in a similar manner to that described in Reference Example 9, but using the appropriate quantity of methyl 3-cyclopentylidene-methyl-4-methoxybenzoate (prepared as described in Reference Example 11), there is prepared 3-cyclopentylidenemethyl-4-methoxybenzoic acid in the form of a white solid, m.p. 156-158°C.

REFERENCE EXAMPLE 13

By proceeding in a similar manner to that described in Reference Example 3, but using the appropriate quantity of 3-cyclopentylidenemethyl-4-methoxybenzoic acid (prepared as described in Reference Example 12), there is prepared 3-cyclopentylidenemethyl-4-methoxybenzoyl chloride in the form of a brown oil, which is used without further purification.

REFERENCE EXAMPLE 14

By proceeding in a similar manner to that described in Reference Example 11, but using isopropyltriphenylphosphonium iodide as reagent instead of cyclopentyltriphenylphosphonium bromide, there is prepared methyl 3-(2-methylpropenyl)-4-methoxybenzoate in the form of a white solid, m.p. 52-53°C.

REFERENCE EXAMPLE 15

By proceeding in a similar manner to that described in Reference Example 9, but using the appropriate quantity of methyl 3-(2-methylpropenyl)-4-methoxybenzoate (prepared as described in Reference Example14), there is prepared 3-(2-methylpropenyl)-4-methoxybenzoic acid in the form of a white solid, m.p. 170-173°C.

REFERENCE EXAMPLE 16

By proceeding in a similiar manner to that described in Reference Example 3, but using the appropriate quantity of 3-(2-methylpropenyl)-4-methoxybenzoic acid (prepared as described in Reference Example 15), there is prepared 3-(2-methylpropenyl)-4-methoxybenzoyl chloride in the form of a brown oil, which is used without further purification.

REFERENCE EXAMPLE 17

Potassium carbonate (3.03 g) is added portionwise to a solution of methyl 3-formyl-4-hydroxy benzoate (3 g) (prepared as described in Y. Suzuki

and H. Takahashi, Chem. Pharm. Bull. 31, 1751 (1983) in dry dimethylformamide (30 mL), followed by the addition of benzyl bromide (3.25 g). The resulting mixture is heated to 60°C for 15 hours. On cooling the resulting precipitate is filtered off, washed with ether and the combined filtrates evaporated under reduced pressure. The resulting residue is partitioned between water (50 mL) and diethyl ether (25 mL). The layers are thoroughly stirred, separated and the aqueous phase further extracted with diethyl ether (2 x 25 mL). The combined organic extracts are dried over magnesium sulphate, evaporated, and the resulting residue is purified by flash chropmatography on silica gel, eluting with ethyl acetate and pentane (7:3 v/v) to give methyl 3-formyl-4-benzyloxybenzoate in the form of white solid, m.p. 76-78°C.

REFERENCE EXAMPLE 18

By proceeding in a similar manner to that described in Reference Example 11, but using the appropriate quantity of methyl 3-formyl-4-benzyloxybenzoate (prepared as described in Reference Example 17), there is prepared methyl 3-cyclopentylidenemethyl-4-benzyloxy benzoate in the form of a colourless oil.

REFERENCE EXAMPLE 19

A solution of methyl 3-cyclopentylidenemethyl-4-benzyloxybenzoate (1.09 g) (prepared as described in Reference Example 18) in dry ethanol (100 mL) containing Palladium on Carbon (10%, 80 mg) is hydrogenated at room temperature and atmospheric pressure. After 3 hours the mixture is filtered through a dry bed of diatomaceous earth and the filtrate is evaporated to give methyl 3-cyclopentylmethyl-4-hydroxybenzoate (0.7 g) in the form of a colourless oil, which is used without further purification.

REFERENCE EXAMPLE 20

A solution of methyl 3-cyclopentylidenemethyl-4-hydroxybenzoate (0.7 g) (prepared as described in Reference Example 19) in dry dimethylformamide (20 mL) is treated with potassium carbonate (0.53 g) and potassium iodide (0.2 g). Chlorodifluoromethane is then bubbled through the

reaction mixture at a very slow rate and the reaction mixture is then heated at 70-75°C for 4.5 hours. The mixture is then treated with water (15 mL) and extracted with ethyl acetate (4 x 15 mL). The combined ethyl acetate extracts are dried over magnesium sulphate, evaporated and the residue is purified by flash chromatography on silica gel eluting with diethyl ether and pentane (3:7 v/v) to give methyl 3-cyclopentylidenemethyl-4-difluoromethoxybenzoate (0.24 g) in the form of a colourless oil.

REFERENCE EXAMPLE 21

By proceeding in a similar manner to that described in Reference Example 9, but using the appropriate quantity of methyl 3-cyclopentylidene-methyl-4-difluoromethoxybenzoate (prepared as described in Reference Example 20), there is prepared 3-cyclopentylidenemethyl-4-difluoromethoxybenzoic acid in the form of a white solid m.p. 114-115°C.

REFERENCE EXAMPLE 22

By proceeding in a similar manner to that described in Reference Example 3, but using the appropriate quantity of 3-cyclopentylidenemethyl-4-difluoromethoxybenzoic acid (prepared as described in Reference Example 21), there is prepared 3-cyclopentylid enemethyl-4-difluoromethoxybenzoyl chloride in the form of a brown oil, which is used without further purification.

REFERENCE EXAMPLE 23

To a solution of N-(3,5-dichloropyrid-4-yl)-3-cyclopentanecarbonyl-4-methoxybenzamide (1.97 g, prepared as described in Reference Example 2) in a mixture of ethanol (15 mL) and tetrahydrofuran (15 mL) is added sodium borohydride (0.12 g). The resulting suspension is stirred at room temperature for 1 hour. Water is then added (150 mL) followed by ethyl acetate (50 mL). The layers are throughly stirred, separated and the aqueous layer is further extracted with ethyl acetate (50 mL). The combined organic extracts are washed with brine (2 x 10 mL), dried over magnesium sulphate and evaporated. The resulting residue is purified by flash chromatography on silica gel, using a mixture of ethyl acetate and cyclohexane (9:11 v/v) to give N-(3,5-

dichloropyrid-4-yl)-3-cyclopentylhydroxymethyl-4-methoxybenzamide (1.34 g) in the form of a white solid, m.p. 90°C.

REFERENCE EXAMPLE 24

By proceeding in a similar manner to that described in Reference Example 5, but using the appropriate quantity of 4-bromo-2-hydroxyacetophenone, there is prepared 4-bromo-2-cyclopentyloxy-acetophenone in the form of an off white solid, m.p. 55-56°C.

REFERENCE EXAMPLE 25

A mixture of 4-bromo-2-cyclopentyloxyacetophenone (13.03 g, prepared as described in Reference Example 24 or as described in F. C. Chen and C. T. Chang, J. Chem. Soc., 148 (1958), copper (I) cyanide (5.15 g) and copper (II) sulphate (0.05 g) in dry dimethylformamide (39 mL) is heated to between 160-170°C for 6.5 hours. After allowing to cool, ferric chloride hexahydrate (19.7 g) and concentrated hydrochloric acid (4.9 mL) in water (160 mL) is added, and the mixture is then heated to 40°C for 20 minutes. After allowing to cool, the mixture is then filtered and the aqueous fitrate extracted with diethyl ether (4 x 50 mL). The combined organic extracts are washed with water (2 x 50 mL), followed by saturated aqueous sodium hydrogen carbonate solution (50 mL), then dried over magnesium sulphate and evaporated to give 4-acetyl-3-cyclopentyloxybenzamide (8.84 g), initially as a brown oil that slowly solidifies to a dark yellow solid, m.p. 188-190°C.

REFERENCE EXAMPLE 26

To a solution of sodium hydroxide (12.92 g) in a mixture of water (32 mL) and ethanol (65 mL) at reflux is added 4-acetyl-3-cyclopentyloxybenzamide (6.46 g, prepared as described in Reference Example 25). The resulting solution is maintained under reflux for 3 hours, after which it is allowed to cool. Water is then added (90 mL) and the mixture concentrated to low bulk. Concentrated hydrochloric acid is then added (until pH 2).The resulting yellow solid is filtered off and recrystallised from a mixture of dichloromethane and peteroleum ether 80-100°C to give 4-acetyl-3-cyclopentyloxybenzoic acid

(4.48 g) in the form of yellow crystals, m.p. 154-158°C.

REFERENCE EXAMPLE 27

By proceeding in a similar manner to that described in Reference Example 3, but using the appropriate quantity of 4-acetyl-3-cyclopentyloxy-benzoic acid (prepared as described in Reference Example 26), there is prepared 4-acetyl-3-cyclopentyloxybenzoyl chloride in the form of a brown oil, which is used without further purification.

REFERENCE EXAMPLE 28

By proceeding in a similar manner to that described in Example 2, but using the appropriate quantity of 4-acetyl-3-cyclopentylbenzoyl chloride (prepared as described in Reference Example 27), there is prepared N-(3,5-dichloropyrid-4-yl)-4-acetyl-3-cyclopentyloxybenzamide in the form of a pale yellow solid, m.p. 120-121.5°C.

REFERENCE EXAMPLE 29

By proceeding in a manner similar to that described in Reference Example 23, but using the appropriate quantity of N-(3,5-dichloropyrid-4-yl)-4-acetyl-3-cyclopentyloxybenzamide (prepared as described in Reference Example 28), there is prepared N-(3,5-dichloropyrid-4-yl)-4-(1-hydroxyethyl)-3-cyclopentyloxybenzamide in the form of a off white solid, m.p. 157-158.5°C.

The compounds of formula I exhibit useful pharmacological activity and accordingly are incorporated into pharmaceutical compositions and used in the treatment of patients suffering from certain medical disorders. More especially, they are cyclic AMP phosphodiesterase inhibitors, in particular type IV cyclic AMP phosphodiesterase inhibitors. The present invention provides compounds of formula I, and compositions containing compounds of formula I, which are of use in a method for the treatment of a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of cyclic AMP phosphodiesterase. For example, compounds within the present invention are useful as bronchodilators and asthma-prophylactic agents and agents for the inhibition of eosinophil accumulation and of the

function of eosinophils, such as for the treatment of inflammatory airways disease, especially reversible airway obstruction or asthma, and for the treatment of other diseases and conditions characterized by, or having an etiology involving, morbid eosinophil accumulation. As further examples of conditions which can be ameliorated by the administration of inhibitors of cyclic AMP phosphodiesterase such as compounds of formula I there may be mentioned inflammatory diseases, such as atopic dermatitis, urticaria, allergic rhinitis, psoriasis, rheumatic arthritis, ulcerative colitis, Crohn's disease, adult respiratory distress syndrome and diabetes insipidus, other proliferative skin diseases such as keratosis and various types of dermatitis, conditions associated with cerebral metabolic inhibition, such as cerebral senility, multi-infarct dementia, senile dementia (Alzheimer's disease), and memory impairment associated with Parkinson's disease, and conditions ameliorated by neuroprotectant activity, such as cardiac arrest, stroke, and intermittent claudication. A special embodiment of the therapeutic methods of the present invention is the treating of asthma.

The compounds are also inhibitors of tumor necrosis factor, especially a-TNF. Thus, the present invention provides compounds of formula I, and compositions containing compounds of formula I, which are of use in a method for treating a patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of TNF-alpha. For example compounds of the present invention are useful in joint inflammation, arthritis, rheumatoid arthritis and other arthritic conditions such as rheumatoid spondylitis and osteoarthritis. Additionally, the compounds are useful in treatment of sepsis, septic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, asthma and other chronic pulmonary diseases, bone resorption diseases, reperfusion injury, graft vs. host reaction and allograft rejection. Furthermore, the compounds are useful in the treatment of infections such as viral infections and parasitic infections, for example malaria such as cerebral malaria, fever and myalgias due to infection, HIV, AIDS, cachexia such as cachexia secondary to AIDS or to cancer. Other disease states that may be treated with the compounds of the present invention include Crohn's disease, ulcerative colitis, pyresis, systemic lupus erythematosus, multiple sclerosis, type I diabetes mellitus, psoriasis, Beçhet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease and leukemia. A special embodiment of the

therapeutic methods of the present invention is the treating of joint inflammation.

According to a further feature of the invention there is provided a method for the treatment of a human or animal patient suffering from, or subject to, conditions which can be ameliorated by the administration of an inhibitor of cyclic AMP phosphodiesterase or of TNF, especially TNF-alpha, for example conditions as hereinbefore described, which comprises the administration to the patient of an effective amount of compound of formula I or a composition containing a compound of formula I. "Effective amount" is meant to describe an amount of compound of the present invention effective in inhibiting cyclic AMP phosphodiesterase and/or TNF and thus producing the desired therapeutic effect.

The present invention also includes within its scope pharmaceutical formulations which comprise at least one of the compounds of formula I in association with a pharmaceutically acceptable carrier or coating.

In practice compounds of the present invention may generally be administered parenterally, rectally or orally, but they are preferably administered by inhalation.

The products according to the invention may be presented in forms permitting administration by the most suitable route and the invention also relates to pharmaceutical compositions containing at least one product according to the invention which are suitable for use in human or veterinary medicine. These compositions may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavorings, colorings, or stabilizers in order to obtain pharmaceutically acceptable preparations.

The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the product, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used.

For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as sterile aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solutions, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration.

Suitable compositions containing the compounds of the invention may be prepared by conventional means. For example, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula I.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.001 to about 50, preferably about 0.001 to about 5, mg/kg body weight per day by inhalation, from about 0.01 to about 100, preferably 0.1 to 70, more especially 0.5 to 10, mg/kg body weight per day by oral administration, and from about 0.001 to about 10, preferably 0.01 to 1, mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subject to be treated, such as age, weight, general state of health and other characteristics which can influence the efficacy of the medicinal product.

The products according to the invention may be administered as frequently as necessary in order to obtain the desired therapeutic effect. Some patients may respond rapidly to a higher or lower dose and may find much weaker maintenance doses adequate. For other patients, it may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day. It goes without saying that, for other patients, it will be necessary to prescribe not more than one or two doses per day.

Compounds within the scope of the present invention exhibit marked pharmacological activities according to tests described in the literature which tests results are believed to correlate to pharmacological activity in humans and other mammals. The following pharmacological test results are typical characteristics of compounds of the present invention.

1. Inhibitory effects of compounds on PDE activity.

1.1 Preparation of PDE isozymes from pig aorta.

The method is described fully by Souness and Scott (Biochem. J., 291, 389-395,1993). Briefly, aortas of freshly slaughtered pigs are placed in Hepes buffered krebs solution, extraneous tissue on the outside of the aorta is trimmed off and the endothelial layer on the intimal surface is removed by rubbing with a cotton swab. Smooth muscle strips are plucked from the aorta and 25 g are homogenized using a Waring Blender in homogenization buffer (20 mM Tris/HCl, pH 7.5, 2 mM $MgCl_2$, 1 mM dithiothreitol, 5 mM EDTA and 1mg/ml aprotinin). The homogenate is further homogenized with an Ultra-Turrax and then centrifuged (3000 g, 5 minutes). The supernatant is removed, and the pellet is sonicated in a small volume (25-50 mL) of homogenization buffer. The sonicate is centrifuged (3000 g, 5 minutes), the pellet discarded and the supernatant is pooled with that from the first centrifugation step. The pooled supernatants are centrifuged (100,000 g, 1 hour), the resulting high-speed supernatant is filtered (0.45 microm) and then applied to a DEAE-trisacryl (IBF) column (50 x 2.44 cm) preequilibrated in column buffer (20 mM Tris/HCl, pH 7.5, 2 mM $MgCl_2$, 1 mM dithiothreitol, 20 microM TLCK). The column is washed with 500-700 mL of column buffer and PDE activities are eluted with 2 successive linear gradients of NaCl (0-200 mM, 400 mL and 200-300 mM, 200 mL) in column buffer. The fractions in the separated peaks of activity corresponding to the different PDE isozymes are pooled and stored at -20°C in 30% (v/v) ethylene glycol.

1.2 Measurement of PDE activity.

PDE activity is determined by the two-step radioisotopic method of Thompson et al., Adv. Cyclic Nucl. Res., 10, 69-92 (1979). The reaction mixture contains 20 mM Tris/HCl (pH 8.0), 10 mM $MgCl_2$, 4 mM 2-mercaptoethanol, 0.2 mM EGTA and 0.05 mg of BSA/ mL. The concentration of substrate is 1 microM.

The IC_{50} values for the compounds examined are determined from concentration-response curves in which concentrations range from 0.1 nM to 40 microM.

1.3 Results.

Compounds within the scope of the invention produce up to about 50% inhibition of porcine aortic cyclic AMP-specific phosphodiesterase (PDE IV) at concentrations from about 10^{-9} M up to about 10^{-5} M, preferably from about 10^{-9} up to about 10^{-8} M. The compounds of the invention are from about 10,000-fold to about 50-fold more selective for cyclic AMP phosphodiesterase IV than cyclic nucleotide phosphodiesterase types I, III or V.

2. Inhibitory effects of compounds on eosinophil superoxide generation.

2.1 Preparation of guinea-pig eosinophils.

The method is described fully in Souness et al (Biochem. Pharmacol., 42, 937-945, 1991).

2.2 Measurement of superoxide generation.

Superoxide anion generation is determined as the superoxide dismutase inhibitable reduction of p-iodonitrotetrazolium violet (INTV) (Souness et al, Biochem. Pharmacol., 42, 937-945, 1991). Briefly, cells are incubated in 96 well microtitre plates in 0.25 mL of Hanks buffered salt solution (HBSS) containing INTV (0.5mg/mL) plus other additions for 45 minutes at 37°C. The cells are then centrifuged at 500 g for 5 minutes and the supernatant is aspirated. The pellet is solubilized by incubation overnight at room temperature in DMSO containing 0.6 M HCl and the absorbance of the reduced dye is measured at 492 nm. The results are expressed in absorbance units.

2.3 Results.

Compounds within the scope of the invention produce up to about 50% inhibition of superoxide generation from eosinophiis harvested from the peritoneal cavities of guinea-pigs at concentrations from about 10^{-8} M to about 10^{-5} M, preferably from about 10^{-8} M up to about 10^{-7} M.

3. Effects of compounds on tracheal smooth muscle contractility.

3.1 Preparation of guinea-pig tracheal strips and contractility studies.

Organ bath studies are performed essentially according to Tomkinson et al. (Br. J. Pharmacol., 108 57-61, 1993). Briefly, tracheas are removed from male, Dunkin-Hartley guinea-pigs (400-500 g) are placed in Krebs Ringer Bicarbonate (KRB) solution and fat and connective tissue are dissected away. Epithelium is removed by mechanical abrasion and the tracheal strips are suspended under an applied load, such that they are at their optimal length, derived from preliminary experiments, and equilibrated for 90 minutes, washing at 15 minute intervals.

Cumulative concentration-response curves to spasmogens are constructed and the concentration producing 30% of maximum contraction (EC_{30}) is determined by computerized linear regression analysis. For relaxant studies, tissues are contracted with spasmogens (such as methacholine, histamine, leukotriene D_4) (EC_{30}) and when the response plateaus, PDE inhibitors (10 nM-100 microM) or vehicle control (DMSO) are added cumulatively. The concentration of relaxant producing 50% inhibition (IC_{50}) of the agonist response is calculated by linear regression. Alternatively, PDE inhibitors, as above, may be added to tissues under basal tone and the concentration producing 50% relaxation (EC_{50}) calculated as above.

3.2 Results.

Compounds within the scope of the invention produce about 50% relaxation of guinea-pig tracheal strips (under basal tone or which had been contracted by treatment with spasmogens) at concentrations from about $5x10^{-9}$ M to about 10^{-5} M, preferably from about $5x10^{-9}$ M to about 10^{-7} M.

4. In vivo bronchodilator actions of compounds.

4.1 Measurement of bronchodilatation.

Bronchorelaxant activity is measured in in vivo tests in the anaesthetized guinea-pig or rat according to the method described in Underwood et al., Pulm. Pharmacol., 5, 203-212, (1992) in which the effects on bronchospasm induced by histamine (or other spasmogens such as methacholine or leukotriene D_4) is determined. Nebulized aerosols generated from aqueous solutions of compounds of the invention are each administered for one minute to the anaesthetized animals. Alternatively, dry powder formulations made up from compounds of the invention and lactose are blown into the airways of the anaesthetized guinea-pigs or rats by the method described in Underwood et al., J. Pharm. Methods, 26, 203-210, 1991.

4.2 Results.

Compounds within the scope of the invention produce from about 30% up to about 90% decrease in bronchospasm when administered at effective doses of about 4 to about 1000 microg/kg, preferably about 4 to about 50 microg/kg, without any significant effect on blood pressure.

5. In vivo actions of compounds on antigen (ovalbamin)-induced eosinophilia in guinea-pigs.

5.1 Treatment of animals and measurement of eosinophil numbers.

Male Dunkin-Hartley guinea-pigs weighing 200-250 g are sensitized using 10 microg ovalbumin in 1 mL of a 100 mg/ mL suspension of aluminium hydroxide, i.p.

Sensitized guinea-pigs are anaesthetised and dry powder formulations of PDE inhibitors or lactose are administered (i.t.) into the airways. In some cases PDE inhibitors are administered orally. 23 hours later the procedure is repeated and 60 minutes later the guinea-pigs are challenged with nebulised saline or ovalbumin (1% in saline) for 15 seconds. 24 hours after challenge

the guinea-pigs are killed and the lungs are lavaged with warm saline. Total and differential cell counts are made.

5.2 Results.

Compounds within the scope of the invention, administered one hour before challenge, inhibit by at least 50% ovalbumin-induced eosinophilia in guinea-pigs which is measured 24 hours after challenge, at oral doses of about 1 to about 50 mg/kg, preferably about 1 to 10 mg/kg and inhaled doses of about 4 to 1000 microg/kg, preferably.4 to 50 microg/kg.

6 In Vitro Inhibitory Effects on TNF-alpha Release by Human Monocytes.

The effects of compounds on TNF-alpha production by human peripheral blood monocytes (PBMs) are examined as follows:

6.1. Preparation of blood leukocytes.

Blood is drawn from normal donors, mixed with dextran, and the erythrocytes allowed to sediment for 35 minutes at 37°C. Leukocytes are fractionated by centrifugation through a discontinuous (18, 20 and 22%) metrizamide gradient. The mononuclear cell fraction comprising 30-40% PBMs is suspended in HBSS and stored at 4°C until use.

6.2. Measurement of TNF-alpha.

Cells from the PBM-rich metrizamide fraction are spun down (200 g for 10 minutes at 20°C), resuspended at 10^6 PBMs/ mL of medium; RPMI 1640 containing 1%v/v FCS, 50 U/ mL penicillin and 50 mg/ mL streptomycin (Gibco, U.K.), then plated out in 96 well plates at 2×10^5 cells/ well. The medium (200 microL) is changed to remove any non-adherent cells and the remaining, adherent PBMs left in the incubator overnight (18 hours). One hour prior to challenge, the medium is changed to that containing compound for test or drug vehicle. Control treatments and compounds for test are assayed in quadruplicate wells. Compounds are tested within the concentration range of 3×10^{-10} M to 3×10^{-6} M. Medium (50 µL) with or without 10ng/ml LPS (E. Coli, 055 B5 from Sigma, U.K.) is then added. The incubation is then

continued for a further 4 hours. Cell supernatants are removed for storage at -20°C.

TNF-alpha levels in cell supernatants are quantified using a standard sandwich ELISA technique. ELISA plates (Costar, U.K.) are coated overnight at 4°C with 3 mg/ mL polyclonal goat anti-human TNF-alpha antibody (British Biotechnology, U.K.) in pH 9.9 bicarbonate buffer. Rabbit polyclonal anti-human TNF-alpha antiserum (Janssen Biochimicha, Belgium) at 1/500 dilution is used as the second antibody and polyclonal goat anti-rabbit IgG horseradish peroxidase (Calbiochem, U.S.A.) at 1/8000 dilution is used as the detection antibody. Color development is measured by absorbance at 450 nm using a Titertek plate reader.

TNF-alpha levels are calculated by interpolation from a standard curve using recombinant human TNF-alpha (British Biotechnology U.K.)(0.125-8 ng/ mL). Data (log-conc. vs. log-resp) are fitted by linear regression ($p > 0.99$) using a Multicalc (Wallac Pharmacia, U.K.) software program. Basal TNF-alpha levels are less than 100 pg/ mL whilst LPS stimulation of the PBMs increases TNF-alpha levels to 3-10 ng/ mL.

6.3 Results.

Compounds within the scope of the invention produce 50% inhibition of LPS-induced TNF-alpha release from human PBMs at concentrations within the range of about 10^{-9} M to about 10^{-6} M., preferably about 10^{-9} M to about 10^{-8} M.

7. Inhibitory effects of compounds on antigen-induced bronchoconstriction in the conscious guinea-pig.

7.1. Sensitisation of guinea-pigs and measurement of antigen - induced bronchoconstriction.

Male, Dunkin-Hartley guinea-pigs (550-700 g) are sensitized as above. Specific airways resistance (SRaw) is measured in conscious animals by whole body plethysmography using a variation of the method of Pennock et al., (J. Appl. Physiol., 46 ,399, 1979). Test compounds or vehicle (lactose carrier)

are instilled into the airways as dry powders through a metal gavage needle. 30 minutes later, the animals are injected with mepyramine (30 mg/kg i.p.) to prevent anaphylactic collapse and placed into the plethysmography chambers where SRaw is determined at 1 minute intervals. Resting SRaw is then determined. Animals are challenged with an aerosol of ovalbumin and SRaw is determined every 5 minutes for 15 minutes.

7.2. Results.

Compounds within the scope of the invention inhibit antigen-induced bronchoconstriction by up to 80% at doses of between about 1 to about 1000 µg/kg (i.t.), preferably about 1 to about 20 µg/kg (i.t.).

8. Inhibitory effects of compounds on serum TNF-alpha levels in LPS - challenged mice.

8.1. Treatment of animals and measurement of murine TNF-alpha.

Female Balb/c mice (age 6-8 weeks, weight 20-22 g from Charles River, U.K.) in groups of five or more animals are dosed p.o. with compounds suspended in 1.5% (w/v) carboxymethyl cellulose then challenged after a minimum period of 30 min with 30 mg of LPS i.p. After 90 min the animals are killed by CO_2 asphyxiation and bled by cardiac puncture. Blood is allowed to clot at 4°C, centrifuged (12,000 g for 5 minutes) and serum taken for TNF-alpha analysis.

TNF-alpha levels are measured using a commercially available murine TNF-alpha ELISA kit, purchased from Genzyme (Cat. no. 1509.00), as recommended by the manufacturer. Values for TNF-alpha are calculated from a recombinant murine TNF-alpha standard curve.

8.2 Results.

Compounds within the scope of the invention inhibit LPS-induced serum TNF-alpha at doses between about 10 and about 10,000 mg/kg, preferably about 10 to about 250 µg/kg.

The value of the compounds of the invention is enhanced by their very low mammalian toxicity levels.

The following Composition Examples illustrate pharmaceutical compositions according to the present invention.

Composition Example 1

5-Cyclopentylmethyl-N-(3,5-dichloropyrid-4-yl)-6-methoxybenzamide (1 g) (mean particle size 3.5 microns) and lactose (99 g) (mean particle size 72 microns) are blended together for 30 minutes in a mechanical shaker/mixer. The resulting blend is filled, to a fill weight of 25 mg, into No.3 hard gelatine capsules, to give a product suitable for use, for example, with a dry powder inhaler.

Composition Example 2

No. 2 size gelatin capsules each containing:-

5-cyclopentylmethyl-N-(3,5-dichloro-pyrid-4-yl)-6-methoxybenzamide	20 mg
lactose	100 mg
starch	60 mg
dextrin	40 mg
magnesium stearate	1 mg

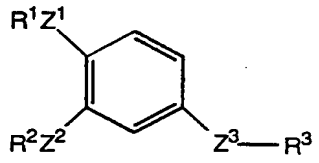
are prepared in accordance with the usual procedure.

Compositions similar to those above are prepared from other compounds of formula I.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof.

WHAT IS CLAIMED:

1. A compound of formula I



I

wherein

R^1 is lower alkyl;

R^2 is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cyclothioalkyl or cyclothioalkenyl;

R^3 is aryl or heteroaryl;

Z^1 and Z^2 are independently oxygen, sulfur or direct bond, and only one of Z^1 and Z^2 is a direct bond;

Z^3 is $-CZCH_2-$ or -CZNH-; and

Z is oxygen or sulfur,

or N-oxide thereof or a pharmaceutically acceptable salt thereof,

provided that

when Z^2 is a direct bond, R^2 is alkyl bonded to the phenyl moiety via a nonquaternary carbon, alkenyl, alkynyl, cyclothioalkyl or cyclothioalkenyl, or R^3 is azaheteroaryl having a nitrogen atom thereof oxidised to the corresponding N-oxide moiety.

2. The compound according to claim 1 wherein

R^2 is alkyl, alkenyl or cycloalkyl;

R^3 is phenyl, substituted phenyl or azaheteroaryl;

Z^1 and Z^2 are independently oxygen or direct bond, and only one of Z^1 and Z^2 is a direct bond; and

Z^3 is $-COCH_2-$ or -CONH-.

3. The compound according to claim 2 wherein

R^1 is methyl, ethyl, fluoroethyl or difluoromethyl;

R^2 is 2-methylpropenyl, cyclopentylfluoromethyl, cyclopentylmethyl, cyclopentyl or trinorbornyl; and

R^3 is azaheteroaryl.

4. The compound according to claim 1 wherein R^3 is azaheterocyclyl having an imine moiety thereof as an N-oxide.

5. The compound according to claim 1 wherein R^3 is phenyl substituted on the 2-position or on both the 2- and 6-positions.

6. The compound according to claim 1 wherein R^3 is heteroaryl substituted on one or both of the positions adjacent to the position of R^3 that is attached to Z^3.

7. The compound according to claim 1 wherein R^3 is azaheteroaryl substituted on one or both, more preferably on both, of the positions adjacent to a position of R^3 that is attached to Z^3.

8. The compound according to claim 7 wherein R^3 is a 3,5-dihalo-pyrid-4-yl.

9. The compound according to claim 8 wherein 3,5-dihalo-1-oxido-4-pyridinium.

10. The compound according to claim 1 wherein Z^2 is -CZNH-.

11. The compound according to claim 10 wherein Z is oxygen.

12. The compound according to claim 1 wherein Z^1 is oxygen and Z^2 is a direct bond; Z^1 is sulfur and Z^2 is a direct bond; or Z^1 is a direct bond and Z^2 is oxygen are preferred.

13. The compound according to claim 12 wherein Z^1 is oxygen and Z^2 is a direct bond.

14. The compound according to claim 1 wherein R^1 is lower alkyl optionally substituted by one or more halo.

15. The compound according to claim 14 wherein the substitutition is on a position of R^1 that is attached to Z^1.

16. The compound according to claim 1 wherein R^2 is lower alkyl, cycloalkyl or cyclothioalkyl optionally substituted by one or more halo.

17. The compound according to claim 1 wherein the substitutition is on a position of R^2 that is attached to Z^2.

18. The compound according to claim 17 wherein R^2 is cyclothioalkyl substituted on a position of R^2 that is attached to Z^2 or on a position adjacent to the thio moiety of the cyclothioalkyl.

19. The compound according to claim 1 wherein R^2 is 2-methylpropenyl, cyclopentylfluoromethyl, cyclopentylmethyl, cyclopentyl, cyclopentylidenemethyl or trinorbornyl.

20. The compound according to claim 1 wherein R^2 is cyclothioalkyl oxidized to the corresponding S-oxide or S,S-dioxide.

21. The compound according to claim 1 wherein R^1 is lower alkyl optionally substituted by halo; and R^2 is 2-methylpropenyl, cyclopentylfluoromethyl, cyclopentylmethyl, cyclopentyl, cyclopentylidenemethyl or trinorbornyl.

22. The compound according to claim 1 which is:

N-(3,5-dichloropyrid-4-yl)-3-cyclopentylmethyl-4-methoxybenzamide;

N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-ethylbenzamide;

N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-methylbenzamide;

N-(3,5-dichloro-1-oxido-4-pyridinio) 3-cyclopentylmethyl-4-methoxybenzamide;

N-(3,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentyloxy-4-ethylbenzamide;

N-(3,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentyloxy-4-methylbenzamide;

N-(,5-dichloro-1-oxido-4-pyridinio)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-ethylbenzamide;

N-(,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentylidenemethyl-4-methoxybenzamide;

N-(,5-dichloro-1-oxido-4-pyridinio)-3-(2-methylpropenyl)-4-methoxybenzamide;

N-(,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentylidenemethyl-4-difluoromethoxybenzamide;

N-(,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentylfluoromethyl-4-methoxybenzamide;

N-(,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentyloxy-4-(1-fluoroethyl)benzamide;

N-(3,5-dichloropyrid-4-yl)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-ethylbenzamide;

N-(3,5-dichloropyrid-4-yl)-3-cyclopentylidenemethyl-4-methoxybenzamide;

N-(3,5-dichloropyrid-4-yl)-3-(2-methylpropenyl)-4-methoxybenzamide;

N-(3,5-dichloropyrid-4-yl)-3-cyclopentylidenemethyl-4-difluoromethoxybenzamide;

N-(3,5-dichloropyrid-4-yl)-3-cyclopentylfluoromethyl-4-methoxybenzamide; or

N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-(1-fluoroethyl)benzamide.

23. The compound according to claim 1 which is:

N-(3,5-dichloropyrid-4-yl)-3-cyclopentylmethyl-4-methoxybenzamide

24. The compound according to claim 1 which is:

N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-ethylbenzamide;

25. The compound according to claim 1 which is:

N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-methylbenzamide;

26. The compound according to claim 1 which is:

N-(3,5-dichloro-1-oxido-4-pyridinio) 3-cyclopentylmethyl-4-methoxybenzamide;

27. The compound according to claim 1 which is:

N-(3,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentyloxy-4-ethylbenzamide;

28. The compound according to claim 1 which is:

N-(3,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentyloxy-4-methylbenzamide;

29. The compound according to claim 1 which is:

N-(,5-dichloro-1-oxido-4-pyridinio)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-ethylbenzamide;

30. The compound according to claim 1 which is:

N-(,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentylidenemethyl-4-methoxybenzamide;

31. The compound according to claim 1 which is:

N-(,5-dichloro-1-oxido-4-pyridinio)-3-(2-methylpropenyl)-4-methoxybenzamide;

32. The compound according to claim 1 which is:

N-(,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentylidenemethyl-4-difluoromethoxybenzamide;

33. The compound according to claim 1 which is:

N-(,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentylfluoromethyl-4-methoxybenzamide;

34. The compound according to claim 1 which is:

N-(,5-dichloro-1-oxido-4-pyridinio)-3-cyclopentyloxy-4-(1-fluoroethyl)benzamide;

35. The compound according to claim 1 which is:

N-(3,5-dichloropyrid-4-yl)-3-(exo)-8,9,10-trinorbornyl-2-oxy-4-ethylbenzamide;

36. The compound according to claim 1 which is:

N-(3,5-dichloropyrid-4-yl)-3-cyclopentylidenemethyl-4-methoxybenzamide;

37. The compound according to claim 1 which is:

N-(3,5-dichloropyrid-4-yl)-3-(2-methylpropenyl)-4-methoxybenzamide;

38. The compound according to claim 1 which is:

N-(3,5-dichloropyrid-4-yl)-3-cyclopentylidenemethyl-4-difluoromethoxybenzamide;

39. The compound according to claim 1 which is:

N-(3,5-dichloropyrid-4-yl)-3-cyclopentylfluoromethyl-4-methoxybenzamide; or

40. The compound according to claim 1 which is:

N-(3,5-dichloropyrid-4-yl)-3-cyclopentyloxy-4-(1-fluoroethyl)benzamide.

41. A pharmaceutical composition comprising a pharmaceutiocally acceptable amount of the compound of claim 1 and a pharmaceutically acceptable carrier.

42. A method for treating a disease state capable of being modulated by inhibiting TNF comprising administering to a patient suffering from said disease state an effective amount of the compound of claim 1.

43. The method of claim 42 wherein said disease state is an inflammatory disease or autoimmune disease.

44. The method of claim 42 wherein said disease state is selected from the group consisting of joint inflammation, arthritis, rheumatoid arthritis, rheumatoid spondylitis and osteoarthritis, sepsis, septic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, asthma, bone resorption diseases, reperfusion injury, graft vs host reaction, allograft rejection malaria, myalgias , HIV, AIDS, cachexia, Crohn's disease, ulcerative colitis, pyresis, systemic lupus erythematosus, multiple sclerosis, type I diabetes mellitus, psoriasis, Beçhet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease and leukemia.

45. The method of claim 44 wherein the disease state is joint inflammation.

46. A method for treating a disease state capable of being modulated by inhibiting production of cyclic AMP phosphodiesterase comprising administering to a patient suffering from said disease state an effective amount of the compound of claim 1.

47. The method of claim 46 wherein said disease state is a pathological condition associated with a function of cyclic AMP phophodiesterase, eosinophil accumulation or a function of the eosinophil.

48. The method of claim 47 wherein said pathological condition is asthma, atopic dermatitis, urticaria, allergic rhinitis, psoriasis, rheumatic arthritis, ulcerative colitis, Crohn's disease, adult respiratory distress syndrome, diabetes insipidus, keratosis, dermatitis, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, cardiac arrest, stroke and intermittent claudication.

49. The method of claim 48 wherein the pathological condition is asthma.

50. A process for preparing the compound of claim 1 substantially as hereinbefore described.

INTERNATIONAL SEARCH REPORT

Inte. .onal Application No
PCT/GB 94/01631

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/75 A61K31/44 C07C235/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 07111 (SMITH-KLINE BEECHAM CORPORATION) 15 April 1993 cited in the application * abstract * ---	1,41
A	WO,A,92 12961 (RHONE POULENC RORER) 6 August 1992 cited in the application * abstract * --- -/--	1,41

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

2

Date of the actual completion of the international search	Date of mailing of the international search report
31 October 1994	11. 11. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/GB 94/01631

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 88, no. 5, 1978, Columbus, Ohio, US; abstract no. 33181e, S. KATSUMI ET AL. 'Fungicides' page 141 ; * RN=65118-18-5; 65118-19-6 * see abstract & JP,A,77 070 019 (HOKKO CHEMICAL INDUSTRY) 10 June 1977 ---	1,2,14, 16
X	CHEMICAL ABSTRACTS. REGISTRY HANDBOOK - NUMBER SECTION. PRINTED ISSUES, COLUMBUS US page 909R 'Number section 1965-1971' * RN=1979-62-0; 1979-63-1 * ---	1,2,14, 16
P,X	WO,A,93 25517 (CELLTECH) 23 December 1993 cited in the application see claim 1 -----	1,41

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB94/01631

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-21, 41-50
because they relate to subject matter not required to be searched by this Authority, namely:

- See attached sheet -

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

(Claims searched completely: 22-40. Claims searched incompletely: 1-21, 41, 50
Claims not searched: 42-49)

Remark: Although claims 42-49 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
The Markish structure in claim 1 is so broad, that a complete search was not possible for economical reasons.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intc. .onal Application No
PCT/GB 94/01631

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9307111	15-04-93	AU-A-	2807192	03-05-93
		CA-A-	2120351	15-04-93
		PT-A-	100928	29-10-93
WO-A-9212961	06-08-92	AU-A-	1188192	27-08-92
		CZ-A-	9301528	13-04-94
		EP-A-	0497564	05-08-92
		EP-A-	0569414	18-11-93
		HU-A-	64942	28-03-94
		JP-T-	6504782	02-06-94
		NZ-A-	241427	26-08-94
JP-A-77070019		NONE		
WO-A-9325517	23-12-93	AU-B-	4347093	04-01-94
		CA-A-	2114114	23-12-93
		EP-A-	0607373	27-07-94
		US-A-	5340827	23-08-94